Synthetic studies towards the ABC-ring system of ijngenol

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SYNTHETIC STUDIES TOWARDS THE ABC-RING SYSTEM OF INGENOL

A THESIS PRESENTED BY

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ABSTRACT

The dried roots of the *Euphobiaceae* plant family is known as "Kan Sui" in Chinese medicine. Kan Sui was recorded as a low-grade drug and used as a herbal remedy for edema, ascites and cancer in mainland China. Examination of *Euphobiaceae* yielded numerous compounds such as ingenol, some derivatives of which have shown powerful anticancer (or cancer), anti-HIV and anti-leukemia activities. Hence, a reliable and efficient synthetic route to ingenol would make it a viable template for new therapeutic agents. However, despite its discovery in the late sixties, ingenol has succumbed to total synthesis only twice. A major challenge to ingenol synthesis is the construction of its highly strained *trans* intrabridge system.

In this thesis a summary of the recent synthetic approaches to the *trans* intrabridge system of ingenol is first reviewed (Chapter 1). An alternative synthetic strategy is then presented. The Type-II intramolecular [4+3] cycloaddition reaction of an oxyallyl cation tethered to the three position of a furan is investigated as means to assemble the [4.4.1] bicyclic skeleton (the AB-ring system) of ingenol. Problems associated with this approach led to a more successful synthetic alternative based on intramolecular enolate alkylation (Chapter II). An alkylidenecarbene selective 1,5 C-H insertion reaction on two oxabicyclic [3.2.1] ketones has been employed as a useful synthetic approach to the AB ring system of ingenol (Chapter III). Attempted substrate directed reduction of a bridgehead double bond is finally investigated as a route to the *trans* ring junction of ingenol (Chapter IV).

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CONTENTS

ABBREVIATIONS

Ac	acetyl
aq.	aqueous
Ar	aryl
atm.	atmospheres
$BH_3.SMe_2$	borane-methyl sulfide complex
9-BBN	9-borabicyclo[3.3.1]nonane
Bu	butyl
Calcd	calculated
°C	degrees celsius
Cp	cyclopentadienyl
Δ	heat
DBU	1,8 diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
dm	decimetre(s)
4-DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact

Et	ethyl
equiv.	equivalent(s)
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
Grubbs II catalyst	Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV)dichloride
h	hour(s)
hν	irradiation with light
*i*Pr	isopropyl
IR	Infra red
KHMDS	potassium bis(trimethylsilyl)amide or potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide or lithium hexamethyldisilazide
L-selectride	lithium tris-*sec*-butylborohydride
LTDM	Lithio(trimethylsilyl)diazomethane
M	molarity
m	meta
M^+	molecular ion
Me	methyl
mg	milligram(s)
min	Minute(s)
mol	mole(s)

m-CPBA	*m*-chloroperoxybenzoic acid
mp	melting point
MeLi	methyllithium
Ms	methanesulfonyl
m/z	mass/charge
N	normal
n	normal
NCS	*N*-chlorosuccinimide
nm	nanometre
NaHMDS	sodium bis(trimethylsilyl)amide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o	ortho
p	para
ppm	parts per million
PPh_3	triphenyl phosphine
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
TFE	trifluoroethanol
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

TLC	thin layer chromatography
TMSCl	chlorotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	tolyl
TMU	1,1,3,3-tetramethylurea
Ts	tosyl

INFRA RED

cm^{-1}	wavenumbers
m	medium
msh	medium shoulder
s	strong
sh	shoulder
vs	very strong
ν_{max}	maximum absorption
w	weak

NUCLEAR MAGNETIC RESONANCE

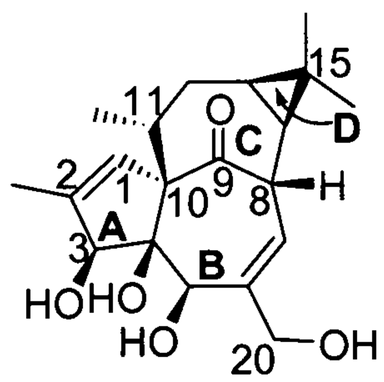
ap	apparent
δ	chemical shift
br	broad
d	doublet
dd	double doublet
ddt	double (double triplet)

dt	double triplet
MHz	megahertz
J	coupling constant
m	multiplet
q	quartet
s	singlet
t	triplet

CHAPTER 1

1.1.0 Ingenol

Ingenol **1** (fig. 1) is a highly oxygenated tetracyclic diterpene isolated from the *Euphorbia ingens* species of the *Euphorbiaceae* plant family by the Hacker group in 1968.[1] The esters of this diterpene (for example the ingenol 3,20-dibenzoate analogues)[2] bind strongly to the regulatory domain of PKC (protein kinase C),[3] thereby exhibiting tumor (or anti-tumor) promoting,[4] anti-leukemia,[5] anti-HIV,[6] nerve growth promoting,[7] pro-inflammatory,[8] and molluscicide[9] activities, testifying to the relevance of this class of diterpenoids for biological and chemical studies. Protein Kinase C is a family of isozymes which play a major role in cellular signal transduction and hence mediate a host of biological responses.[10] To that end, an efficient synthetic access to ingenol would make it a viable template to the development of new therapeutic agents.



1

Figure 1

Besides its biological potential, ingenol is of further interest to natural product chemists, owing to its bewildering structural diversity.[11] It has a polyhydroxylated southern region notably in the *cis*-triol, which represent a formidable synthetic challenge to organic chemists. However, the most challenging obstacle to ingenol

synthesis is the construction of its highly strained "inside-outside" or *trans* intrabridgehead stereochemical relationship between C-8 and C-10 (ingenol numbering). The two bonds flanking the carbonyl bridge adopt a *trans* orientation with one pointing down and the other pointing up, leading to a highly strained system since both bonds are in the same ring.

1.1.1 The inside-outside stereochemistry

There are three different stereoisomers that can be used to describe bridged bicyclic systems, an out-out isomer **2**, an in-in isomer **3** and an in-out isomer **4** (Figure 2).[12]

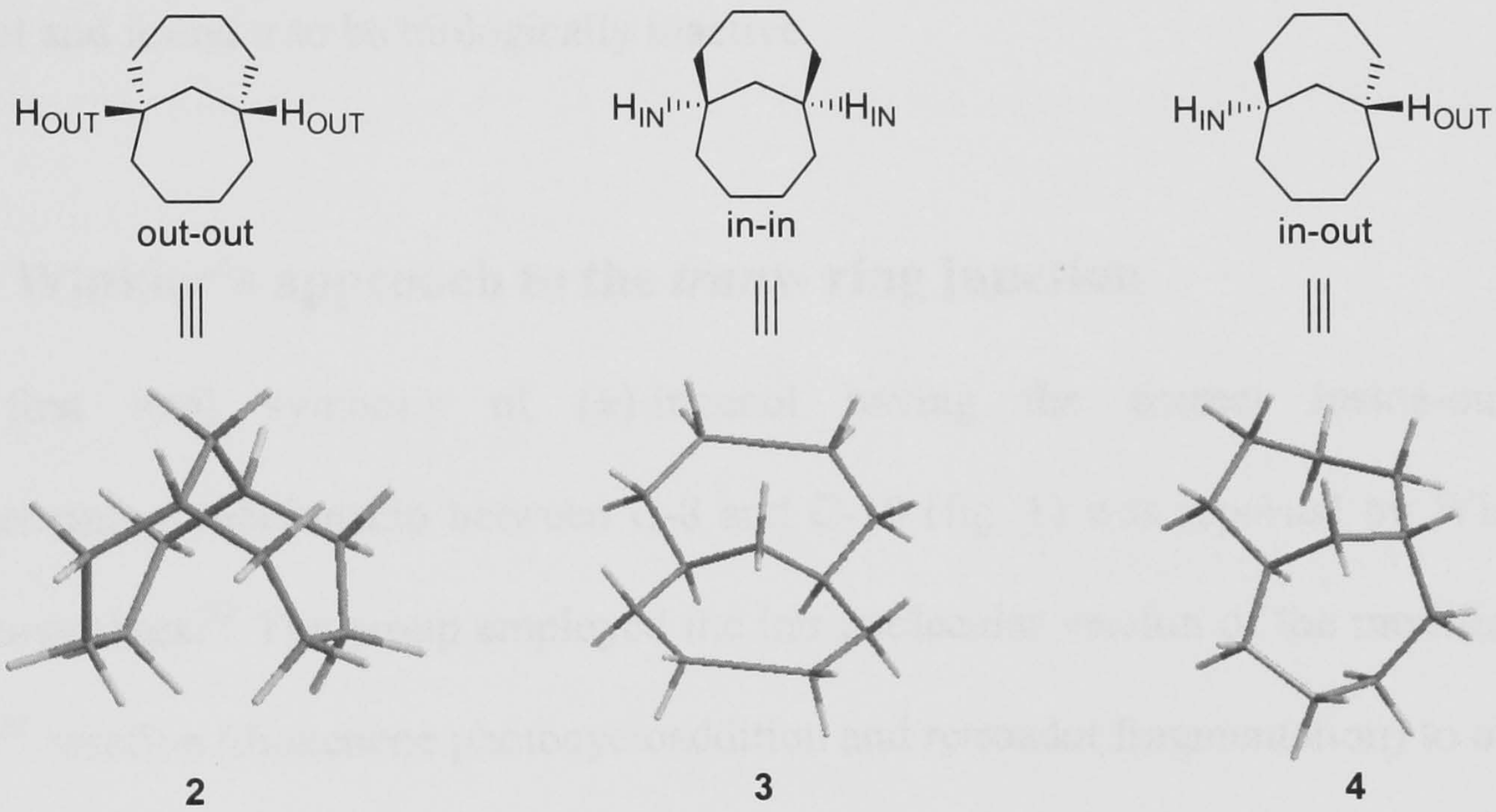


Figure 2

The most unstable isomer is usually the in-in isomer **3** owing to the severe repulsive interaction between the inside atoms. However, the energy difference between the in-out and the out-out isomers varies depending on the bridged system. For example, in-out bicycle [4.4.1]undecane **4** is more strained than its out-out isomer **2** by 6.3 kcal mol^{-1}.[13] Ingenol itself is more strained than its C-8 isoingenol epimer by 5.9 kcal mol

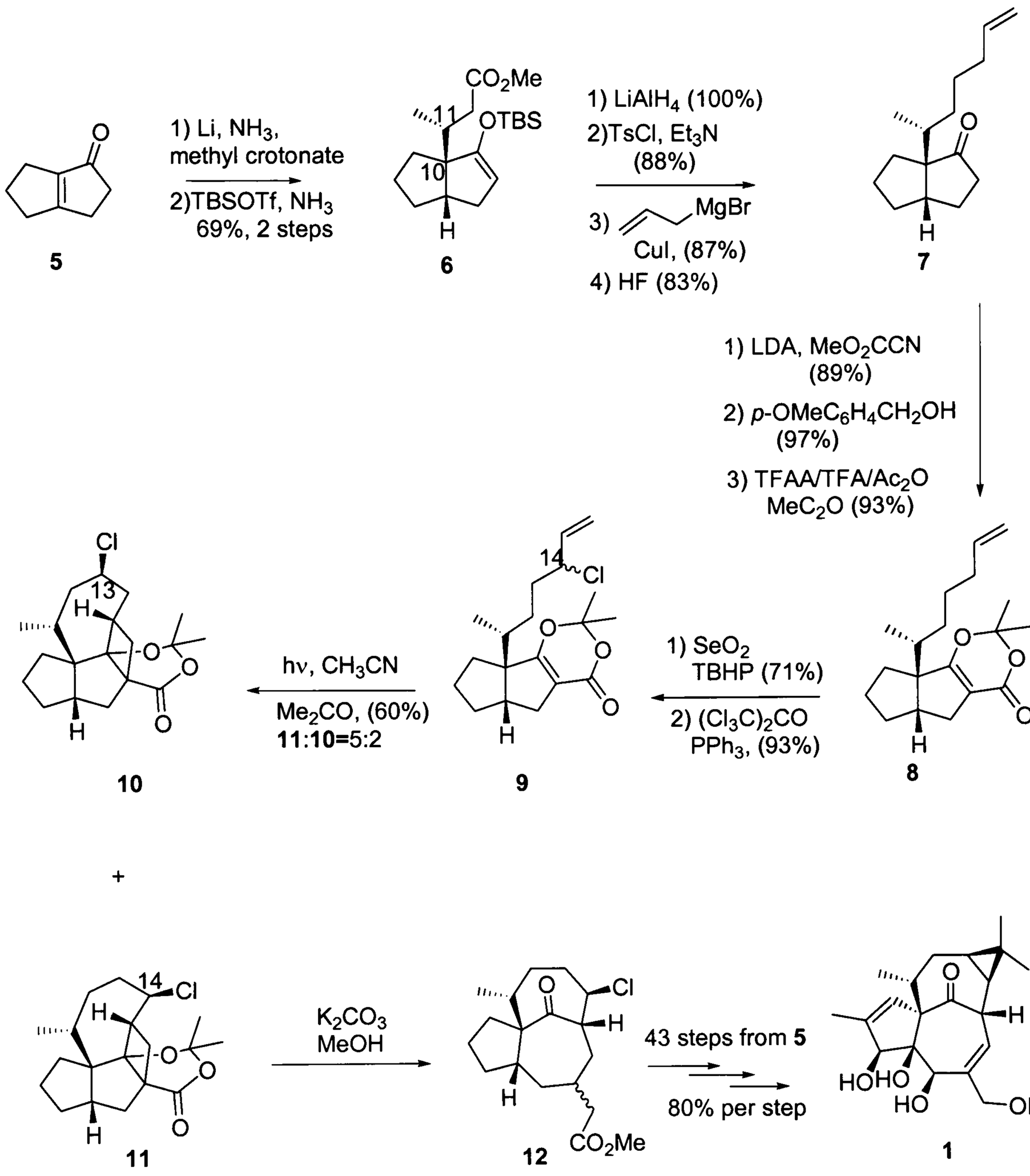
[1].[8] A few other natural products such as taxol and phorbol exhibit this phenomenon of 'inside-outside' stereochemistry.[11]

1.1.2 Synthetic approaches to the 'inside-outside' ring junction

Construction of the highly strained inside-outside ingenane skeleton is such a daunting challenge that it requires a special approach,[14] and to date only the synthetic methods reported by Winkler,[15] Funk,[16] Rigby,[17] Kuwajima,[18] Wood,[19] and Kigoshi[20] have successfully rendered the *trans*-ring junction. The importance of this stereochemistry at the critical junction was demonstrated by Paquette[21] when he synthesised the less strained C-8 epimer possessing the fully functionalised AB ring of ingenol and found it to be biologically inactive.

1.1.3 Winkler's approach to the *trans*- ring junction

The first total synthesis of (±)-ingenol having the correct inside-outside stereochemical relationship between C-8 and C-10 (fig. 1) was reported by Winkler and co-workers.[22] The group employed the intramolecular version of the modified de Mayo[23] reaction (dioxenone photocycloaddition and retroadol fragmentation) to obtain the inside-outside stereochemical relationship between C-8 and C-10 of ingenol.[24] The requisite photosubstrate **9** was prepared as outlined in Scheme 1.



Scheme 1

Michael addition of the enolate derived from dissolving metal reduction of enone **5** to methyl crotonate led, after silylation of the intermediate ketone, to **6** in a 14:1 ratio of α:β C-11 methyl epimers.

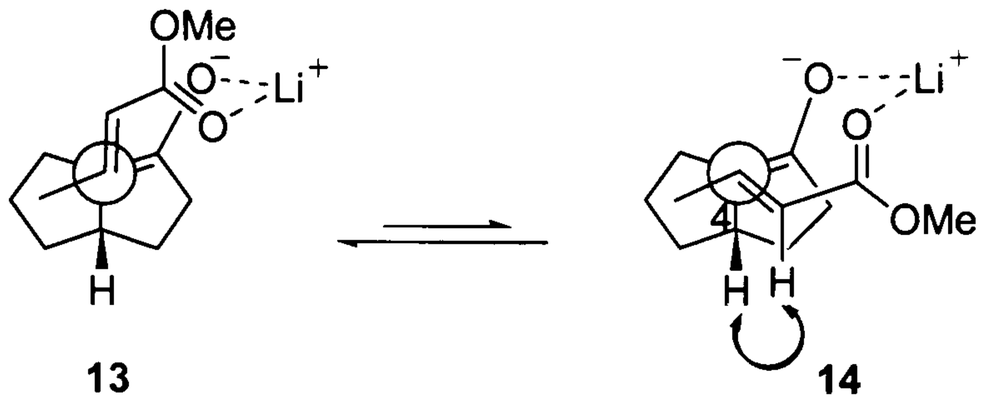
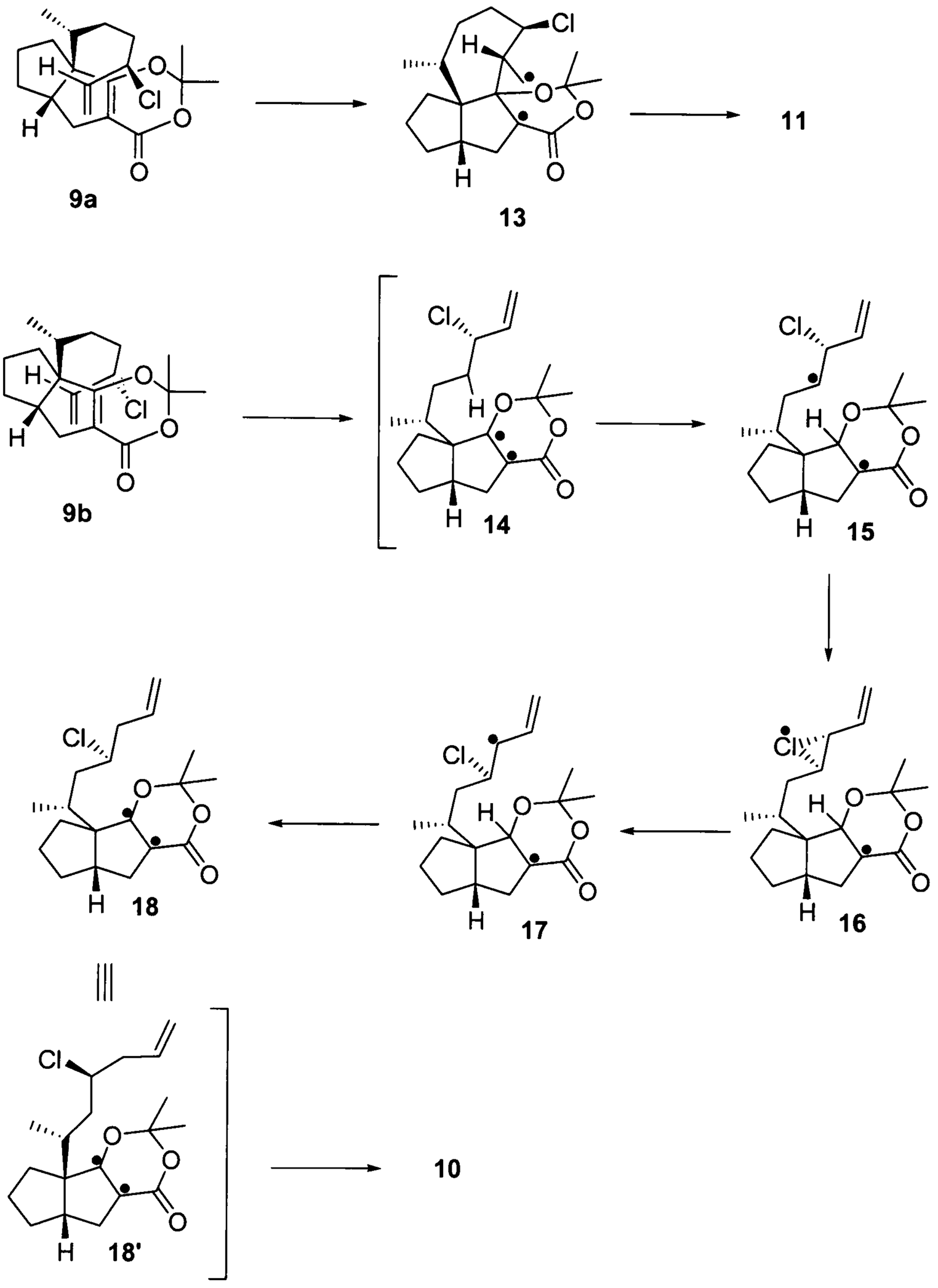


Figure 3

The establishment of the C-10 and C-11 relative stereochemistry is explained by inspection of the chelated transition state structures **13** and **14** in Figure 3. Although, both **13** and **14** experience gauche interactions between the crotonate and the enolate, **14** also suffers from an unfavourable steric interaction between the crotonate α-proton and the C-4 methine of the enolate (Fig. 3) leading to the preferential formation of **6** from **13**.[19] Ester **6** was elaborated upon to dioxenone **9** with a chloride at C-14 to facilitate formation of the ingenol D-ring by a cyclopropanation reaction. Irradiation of a 1:1 mixture of C-14 chloro epimers of **9** led to desired photoadduct **11** and C-13 chloro isomer **10**. Fragmentation of **11** with methanolic potassium carbonate led to ester **12** with the critical *trans*- intrabridged stereochemistry.



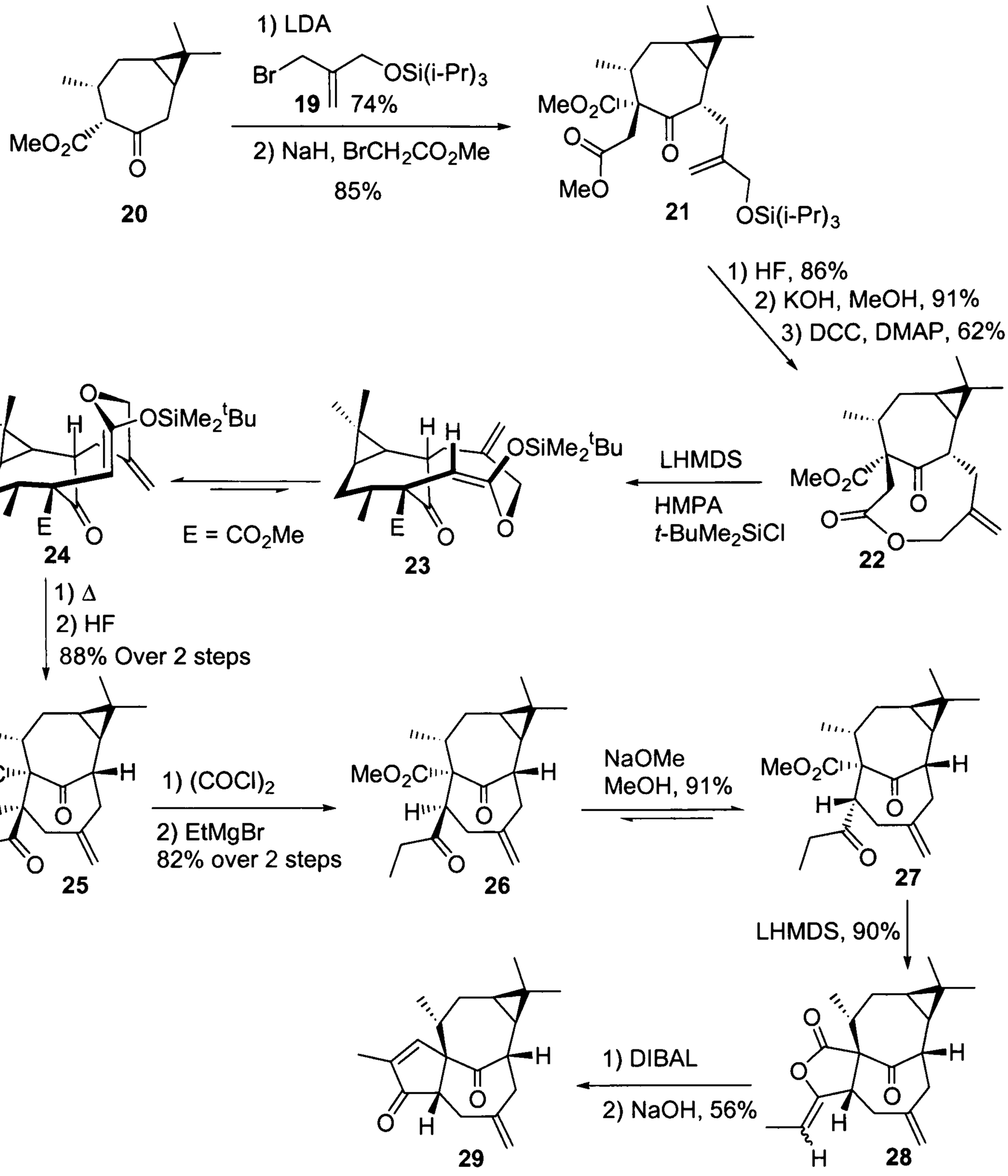
Scheme 2

The selective formation of C-14β chloro photoadduct **11** was attributed to the fact that only the C-14β chloro isomer **9a** (Scheme 2) can lead to **11** via biradical **13** owing to unfavourable interaction in the C-14α epimer **9b**. It was proposed that C-13β chloro isomer **10** was formed from C-14α epimer **9b** via intramolecular hydrogen atom abstraction to give **15** (Scheme 2) which led to diradical **16**. Rearrangement of **16** led to **17**. However, an alternative reaction pathway is elimination of a chloride radical

from **15** to give a diene species which could then be attacked by the chloride radical to give **17**. A second intramolecular hydrogen abstraction of **17** led to **18** (redrawn as **18'**) which underwent a [2+2] photocycloaddition to the C-13β chloro isomer **10**.[25] The total synthesis of ingenol was completed in 45 steps from enone **5** with an 80% average yield per step.

1.1.4 Funk's approach

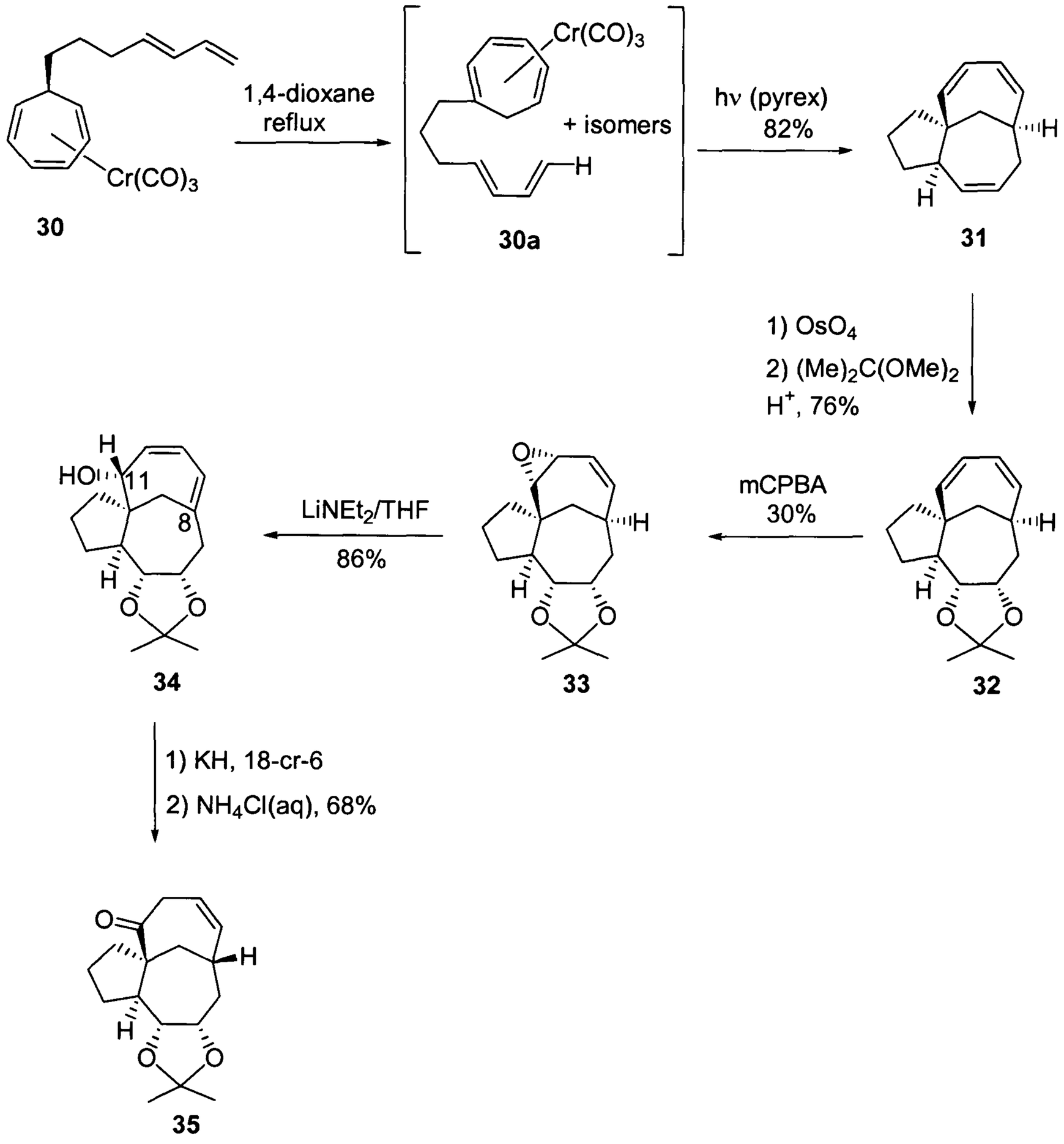
Funk's solution to the inside-outside stereochemistry problem was based on a Claisen rearrangement-ring contraction strategy, **23** to **25** (Scheme 3).[26] The critical inside-outside stereochemistry of C-8 and C-10 (ingenol numbering) was established early in the sequence by using the substituents on the enantiomerically pure cycloheptanone **20** to stereoselectively attach two side chains *trans* to one another as depicted in **21**. Subsequent bond formation between the two side chains resulted in the formation of lactone **22**. Rearrangement of the silyl ketene acetal **23/24** derived from lactone **22** gave the ring contracted *trans*-bridged bicyclo[4.4.1] system of **25**. The formation of **25** was attributed to a transition state arising from conformer **24** which would be much preferred as a result of a through space destabilizing interaction between the ketone and the enol ether oxygen atom in conformer **23**.[27] Claisen product **25** was elaborated upon to the first reported synthesis of a tetracyclic ring system baring the inside-outside stereochemical relationship at C-8 and C-10.



Scheme 3

1.1.5 Rigby's approach

Rigby solved the inside-outside stereochemical problem by a 1,5-H sigmatropic rearrangement of the relatively unstrained and readily accessible outside-outside or *cis*-bicyclo[4.4.1]undecane into the more strained *trans*-isomer.[28]

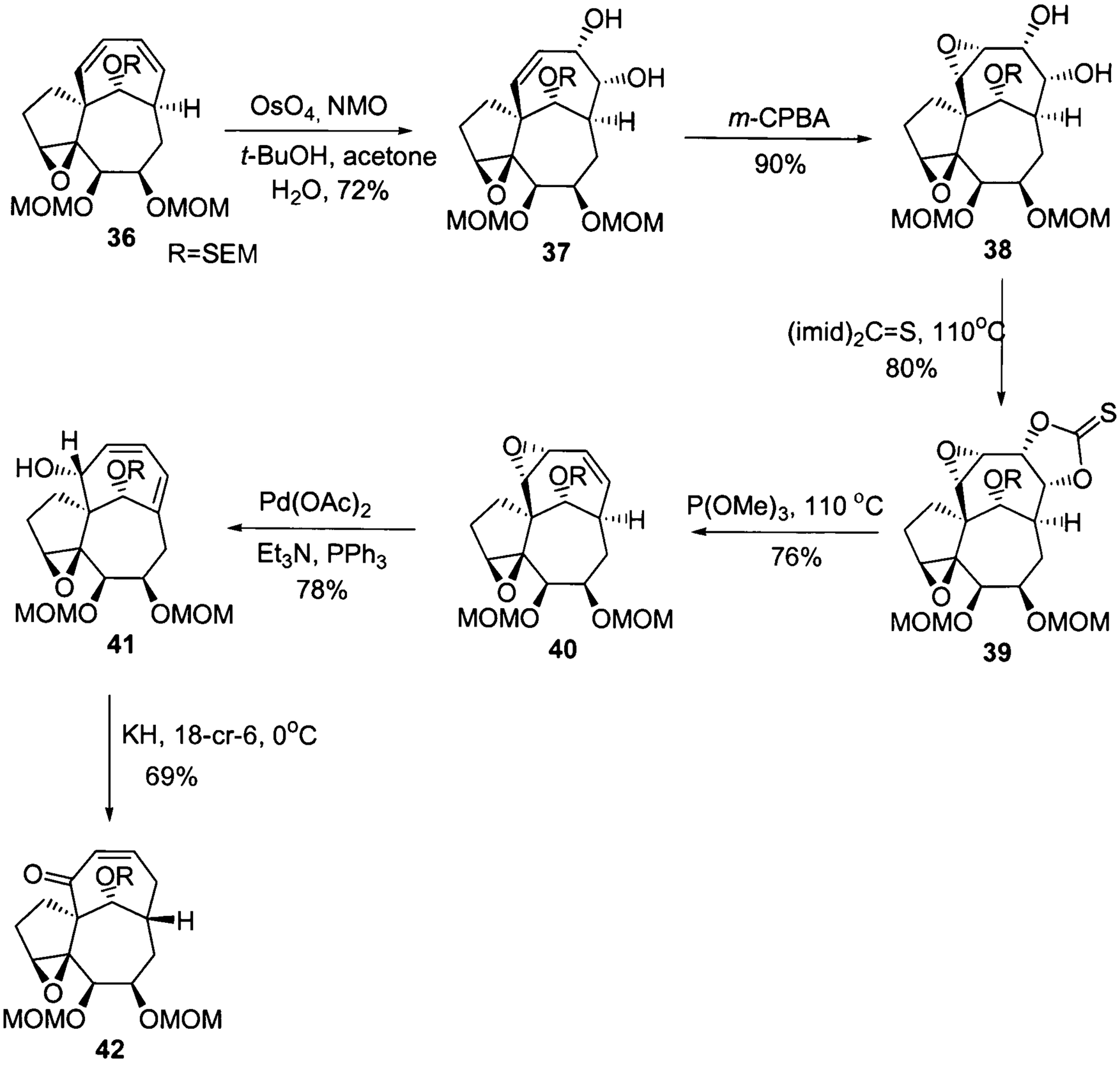


Scheme 4

Conversion of complex **30** to tricycle **31** was achieved by first heating **30** to equilibrate all possible isomers of which owing to geometric constraints only isomer **30a** underwent effective [6+4] photochemical cycloaddition to afford adduct **31** in excellent yield (Scheme 4).[29] A routine *cis*-dihydroxylation of the isolated alkene from the more accessible *exo*-face of the bicyclo[4.4.1]undecane system of **31** followed by protection led to **32**. Epoxidation of the more hindered double bond of **32** from the *exo*-face gave only 30% of the desired epoxide **33**. The epoxide of **33** was opened in a vinylogous fashion to give required dienol **34**. Dienol **34** in the presence of KH and

18-crown-6 effected an alkoxide accelerated 1,5-H sigmatropic rearrangement, delivering the β-H on the alkoxide carbon (C-11) to the bridgedhead position C-8 with retention of stereochemistry to yield the inside-outside bicyclic [4.4.1]undecane system of **35** (Scheme 4).

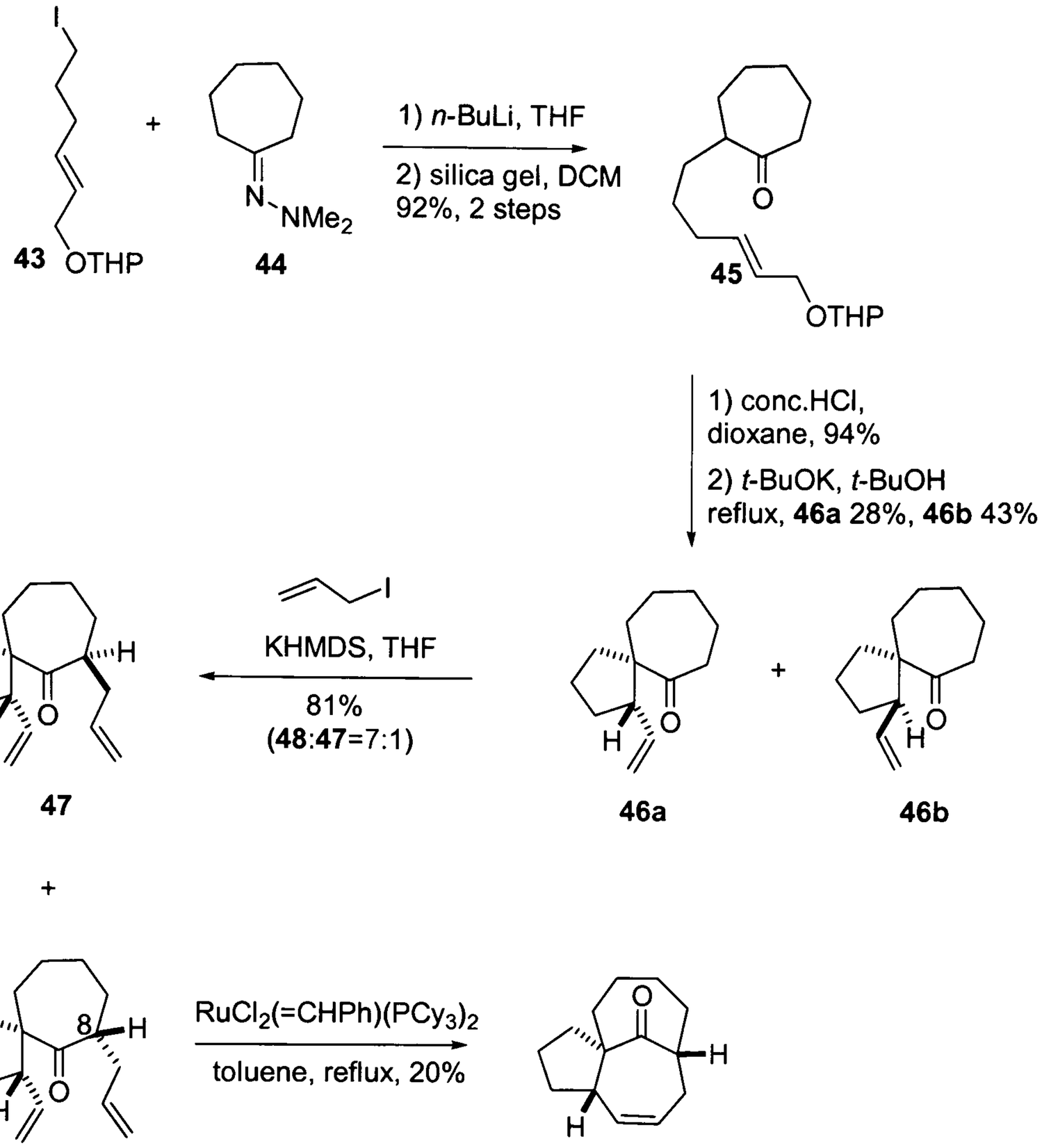
More recently, Rigby reported an improved method for achieving the overall transformation in Scheme 4, which exploits Pd-promoted isomerization of an allylic epoxide into the dienol required for the 1,5-H sigmatropic rearrangement (Scheme 5).[30] Epoxide **40** was prepared from diene **36**, following dihydroxylation of the more accessible double bond from the *exo*-face, epoxidation and olefination. Exposure of **40** to Pd-mediated isomerization conditions gave dienol **41** in good yields. Dienol **41** was converted to the *trans*-intrabridgehead system in **42** under standard conditions.



Scheme 5

1.1.6 Kigoshi's approach

Kigoshi reported the first direct cyclisation to the "inside-outside" tricyclic skeleton of ingenol using a ring closing olefin metathesis reaction.[20] The synthesis of the key intermediate **48** is shown in Scheme 6.



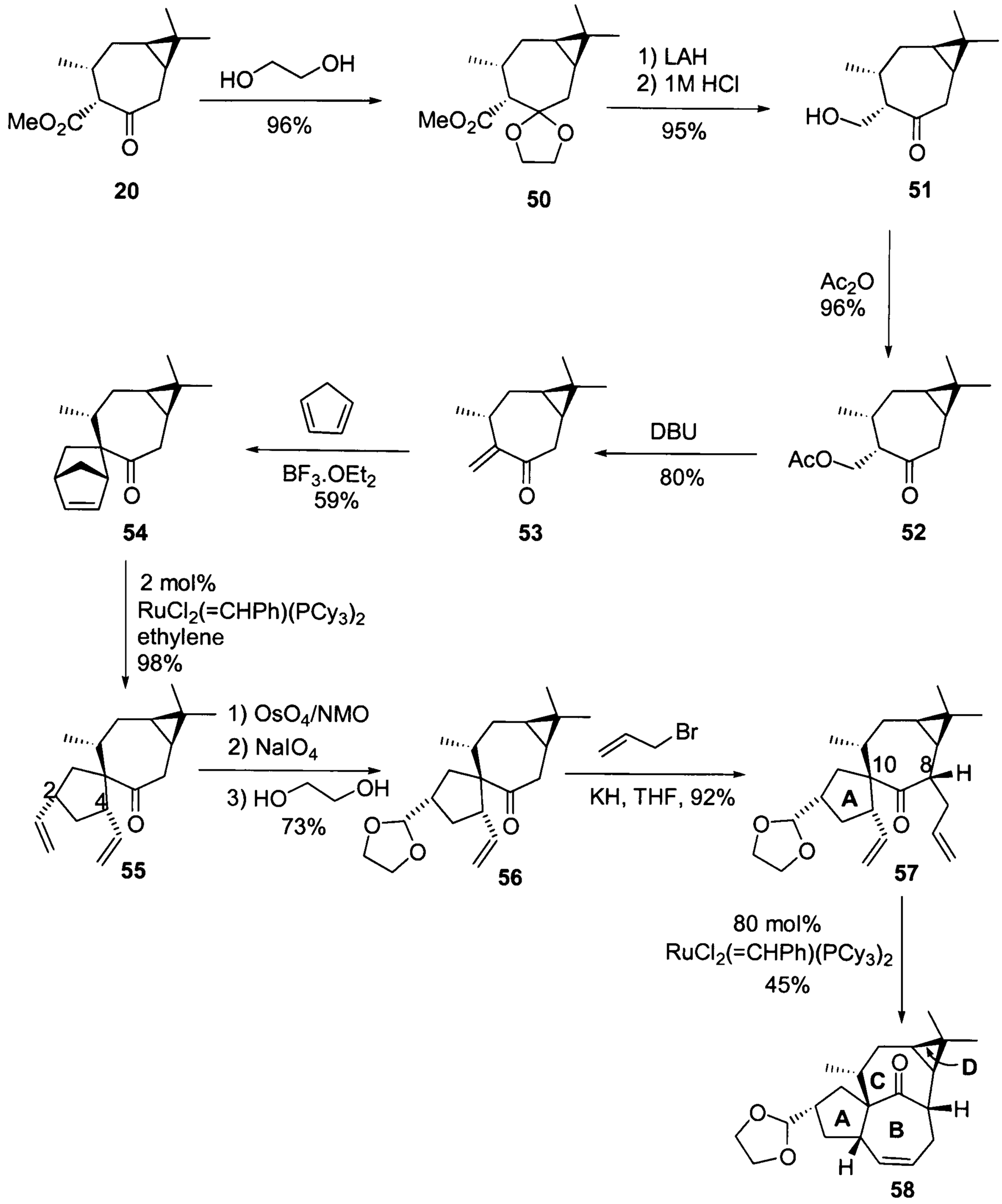
Scheme 6

Intermolecular alkylation of cycloheptanone *N,N*-dimethylhydrazone **44** with ether **43** followed by hydrolysis gave ketone **45**. Treatment of **45** with concentrated hydrochloric acid gave an allylic chloride that was treated with a base to give spiroketones **46a** and **46b** in 28% and 43% yield respectively. Ketone **46a** was allylated to give a 1:7 mixture of allylic ketones **47** and **48** (Scheme 6). The stereochemical outcome was attributed to allylation of **46a** from the less hindered face of the corresponding enolate and therefore allyl ketone **48** with the correct C-8β hydrogen stereochemistry would predominate. Ring-closing metathesis of **48** using Grubbs' ruthenium catalyst in boiling toluene gave *trans* tricyclic ketone **49** in 20%

yield. In contrast, the ring-closing metathesis of **47** under the same reaction conditions afforded the less sterically strained "outside-outside" isomer in 76% yield.

1.1.7 Wood's approach

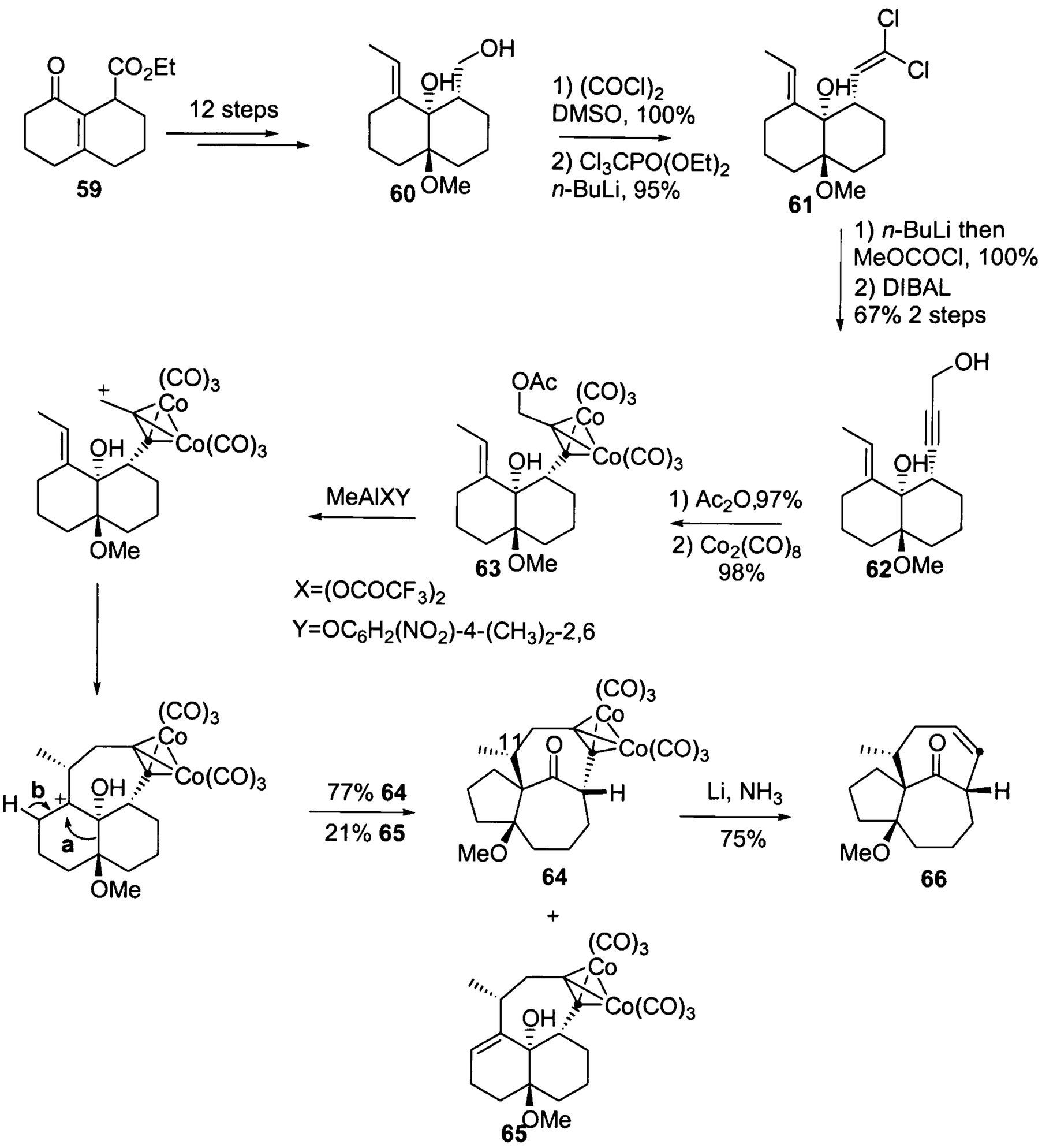
Wood assembled the complete tetracyclic skeleton of ingenol via a tandem ring-opening ring-closing metathesis to close the strained "inside-outside" BC ring system **54** to **58** (Scheme 7).[19] Vinylketone **53** was formed following protection, reduction, deprotection, acetylation and elimination of known β-keto ester **20** (Scheme 7). A Diels-Alder reaction of **53** with cyclopentadiene gave a mixture of diastereomers of which **54** was the major diastereomer. Ring-opening of **54** using Grubbs' catalyst gave **55** which was converted into acetal **56** following regioselective dihydroxylation of the C-2 olefin and cleavage of the corresponding aldehyde. Alkylation of **56** occurred selectively from the more accessible *exo* face of the enolate corresponding to **56** to give the "inside-outside" stereochemical relationship of C-8 and C-10 of **57**. Exposure of **57** to 80 mol% of Grubbs's catalyst in refluxing toluene led to the ABCD tetracyclic "inside-outside" ring system of **58** (Scheme 7).



Scheme 7

1.1.8 Kuwajima's approach

Kuwajima adopted a tandem cyclization-rearrangement strategy for the construction of the highly strained *trans*-bridged BC ring system of ingenol.[18] The synthesis of the tandem cyclization precursor *trans*-decalinol derivative **63** and the subsequent rearrangement is shown in Scheme 8.

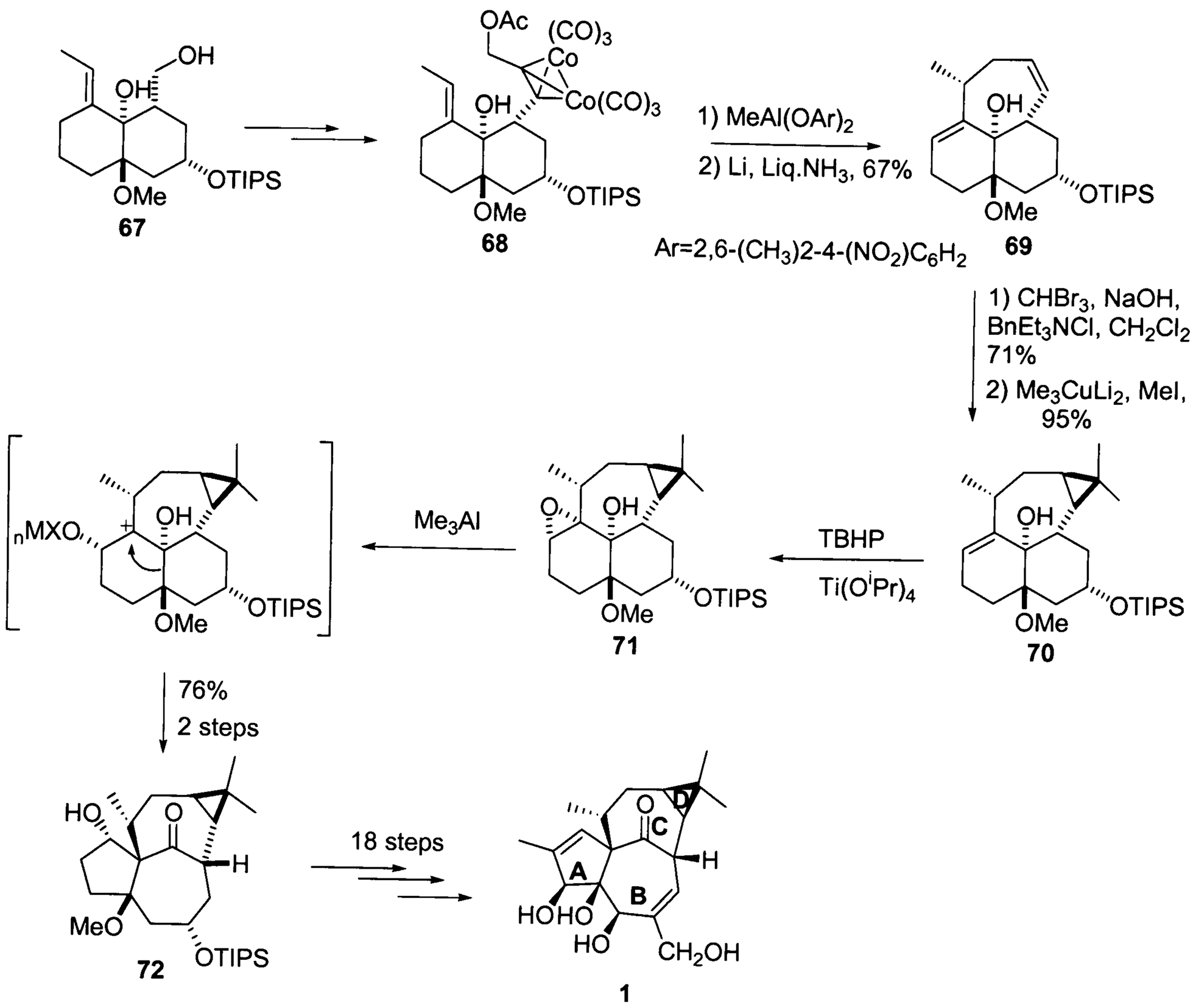


Scheme 8

Trans-Decalinol **60** was made from keto ester **59** in a twelve steps synthesis involving a diastereoselective epoxidation and regioselective hydrolysis of the epoxide. A Swern oxidation of the primary alcohol of **60**, followed by olefination of the corresponding aldehyde gave dichloroalkene **61**. Treatment of **61** with excess butyllithium, followed by methyl chloroformate gave an acetylenic ester that was reduced to propargyl alcohol **62**. Alkyne **62** was converted to the cationic precursor **63** through acetylation and complexation using $Co_2(CO)_8$. A tandem cyclization-rearrangement reaction of **63**

was induced using aluminium 2,6-dimethyl-4-nitrophenoxide to produce tertiary ketone **64** (via path **a**). Formation of **65** was attributed to attack of the dicolbalt hexacarbonyl on the ethylidene carbon to generate the tertiary cation intermediate, which prefers β-elimination (path **b**) rather than rearrangement of the carbon framework (Scheme 8).[28] It is noteworthy that the stereochemistry at C-11 was achieved by using the (*E*)-isomer of the ethylidenedecalin derivative. Deprotection of the dicobalt complex of **64** by Birch reduction gave the inside-outside tricyclic ingenane skeleton of **66** (Scheme 8).

More recently, Kuwajima reported the total synthesis of (±)-ingenol using a new strategy to the inside-outside stereochemical problem based on rearrangement of an epoxy alcohol.[31] The synthetic route to the key intermediate **72** is shown in Scheme 9. Dicobalt acetylene complex **68** was made from *trans*-decalin derivative **67** under similar conditions to that in Scheme 8 (**60** to **63**). Complex **68** underwent cyclisation to allylic alcohol **69** under the influence of methylaluminium bis(2,6-dimethyl-4-nitrophenoxide) and removal of the dicobalt acetylene complex under Birch conditions. The D ring of ingenol was then installed stereoselectively in allyl alcohol **70** by dibromocyclopropanation followed by methylation. Epoxidation of **70** from the more accessible α-face of the double bond of **70** gave epoxide **71**. Metal alkoxide accelerated rearrangement of **71** was effected using trimethylaluminium to the inside-outside tetracyclic skeleton of **72** having the complete ABCD ring system of ingenol (Scheme 9).


OH
OH
OTIPS
OMe
67
OAc
(CO)3
Co
Co(CO)3
OH
OTIPS
OMe
68
1) MeAl(OAr)2
2) Li, Liq.NH3, 67%
Ar=2,6-(CH3)2-4-(NO2)C6H2
OH
OTIPS
OMe
69
1) CHBr3, NaOH,
BnEt3NCl, CH2Cl2
71%
2) Me3CuLi2, MeI,
95%
OH
OTIPS
OMe
70
TBHP
Ti(OiPr)4
O
OH
OTIPS
OMe
71
Me3Al
nMXO
OH
OTIPS
OMe
76%
2 steps
HO
O
H
MeO
OTIPS
72
18 steps
O
D
C
H
A
B
HO
HO
HO
CH2OH

Scheme 9

1.1.9 Summary

Ingenol has biological potential as a therapeutic template for cancer and HIV. Its synthesis has been of considerable challenge to organic chemists for many years. The most formidable of these challenges being the establishment of the highly strained *trans*-intrabridgehead stereochemical relationship within the ingenane skeleton. Although a handful of strategically distinct approaches for addressing this issue have been disclosed, only two have led to racemic total syntheses of ingenol. Furthermore, these synthetic endeavours often involve lengthy transformations and some are inefficient. For example, Kuwajima's[31] approach to racemic ingenol involves 45 steps and Kigoshi's[20] approach yielded only 20% of the *trans*-intrabridgehead ingenane skeleton. While an asymmetric total synthesis of ingenol is still elusive, there is still the need to expand the synthetic repertoire of approaches to ingenol.

1.2.0 Aims and Objectives of the Project

The aim of the project is to investigate a new approach to the *trans*-ring junction of ingenol. This approach is based on three key aspects:

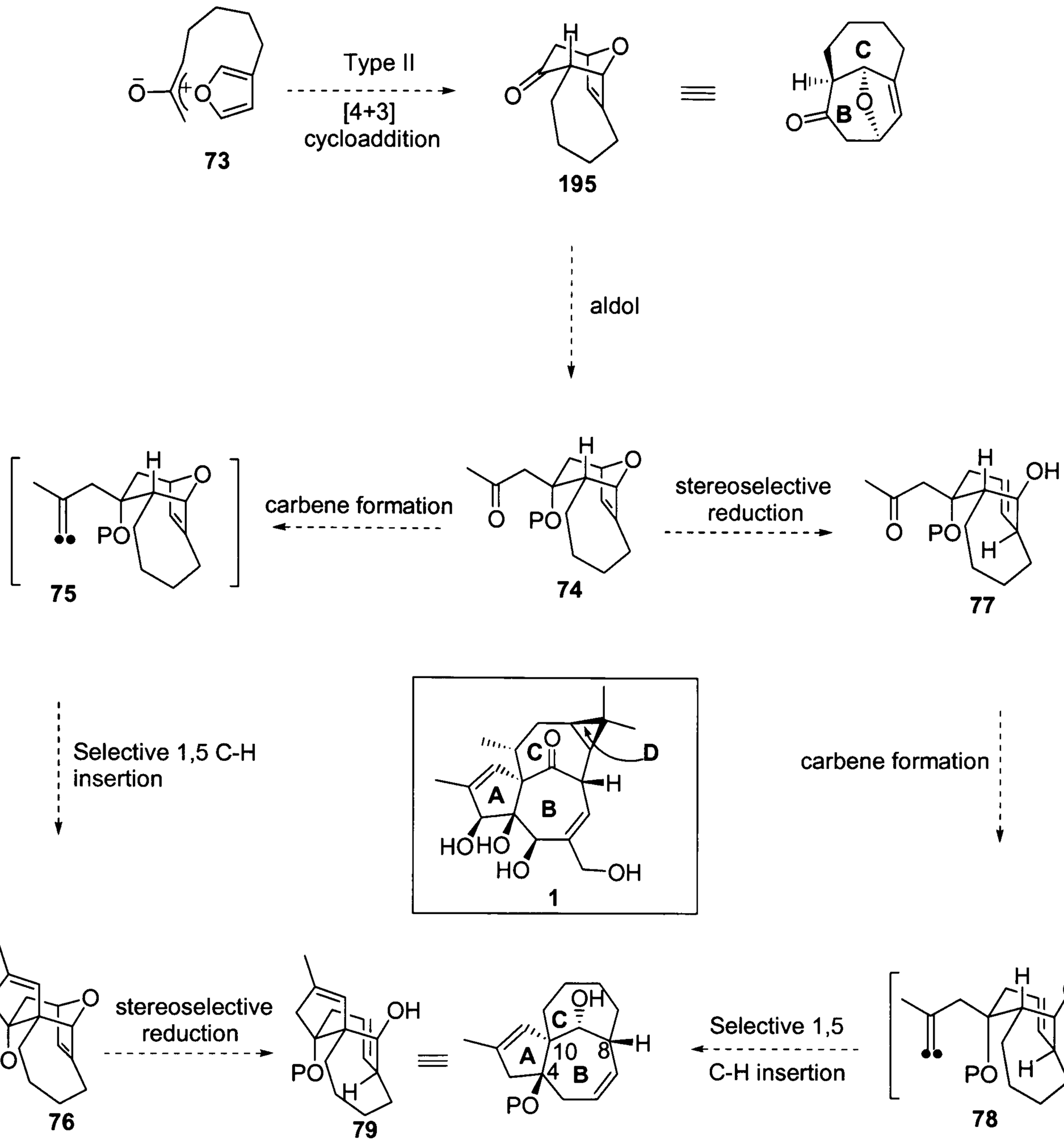
1) an intramolecular Type II [4+3] cycloaddition reaction to assemble the B,C ring system of ingenol (Chapter II),

2) a face selective aldol reaction, as a precursor to a 1,5 C-H alkylidenecarbene insertion reaction to assemble the C ring (Chapter III), and

3) stereoselective reduction of a bridgehead double bond system as means to access the less thermodynamically favourable *trans*-ring junction of ingenol (Chapter IV).

The key bond forming and breaking reactions are shown in Scheme 10. It was anticipated that an intramolecular [4+3] cycloaddition reaction of **73** would furnish bicyclic ketone **195**. An aldol reaction between acetone and bicyclic ketone **195** followed by protection should deliver protected β-hydroxyketone **74**. Ketone **74** could then be converted to alkylidenecarbene **75**. A selective 1,5 C-H insertion of alkylidenecarbene **75** should render the tricyclic ring system of **76**. A stereoselective reduction of the bridgehead double bond of **76** should deliver diene **79** possessing the ABC ring system of ingenol and the correct stereochemistry at C-4, C-8 and C-10 (ingenol numbering).

Alternatively, compound **79** may be prepared by a stereoselective reduction of the bridging double system of **74** to give **77**, followed by alkylidenecarbene formation, and an intramolecular selective 1,5 C-H insertion reaction of **78** (Scheme 10).



Scheme 10

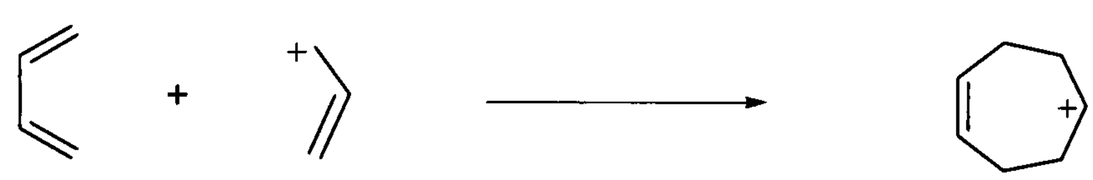
The overall strategy, in addition to establishing the *trans*-ring junction, potentially introduces two alkenes in the correct positions (with respect to the natural product ingenol **1**), and oxygen functionality at C-4 and C-9 (ingenol numbering) that could be used to elaborate further on the carbocyclic skeleton of **79** (Scheme 10).

Further details on each of the steps can be found in the following chapters, along with literature on the chemistry involved.

CHAPTER 2

2.1.0 The [4+3] Cycloaddition Reaction

A [4+3] cycloaddition reaction is a reaction between an allylic cation and a diene. The reaction is a powerful method for the synthesis of seven membered rings (Scheme 11).[32] As a result, the process has great potential for the synthesis of many complex carbocyclic systems found in nature.[33] For this reason, the reaction is of particular interest to many synthetic organic chemists. When the central atom of the allyl cation is attached to a heteroatom for example oxygen (X = O^-, Scheme 12) the allyl cation is known as an oxyallyl cation.

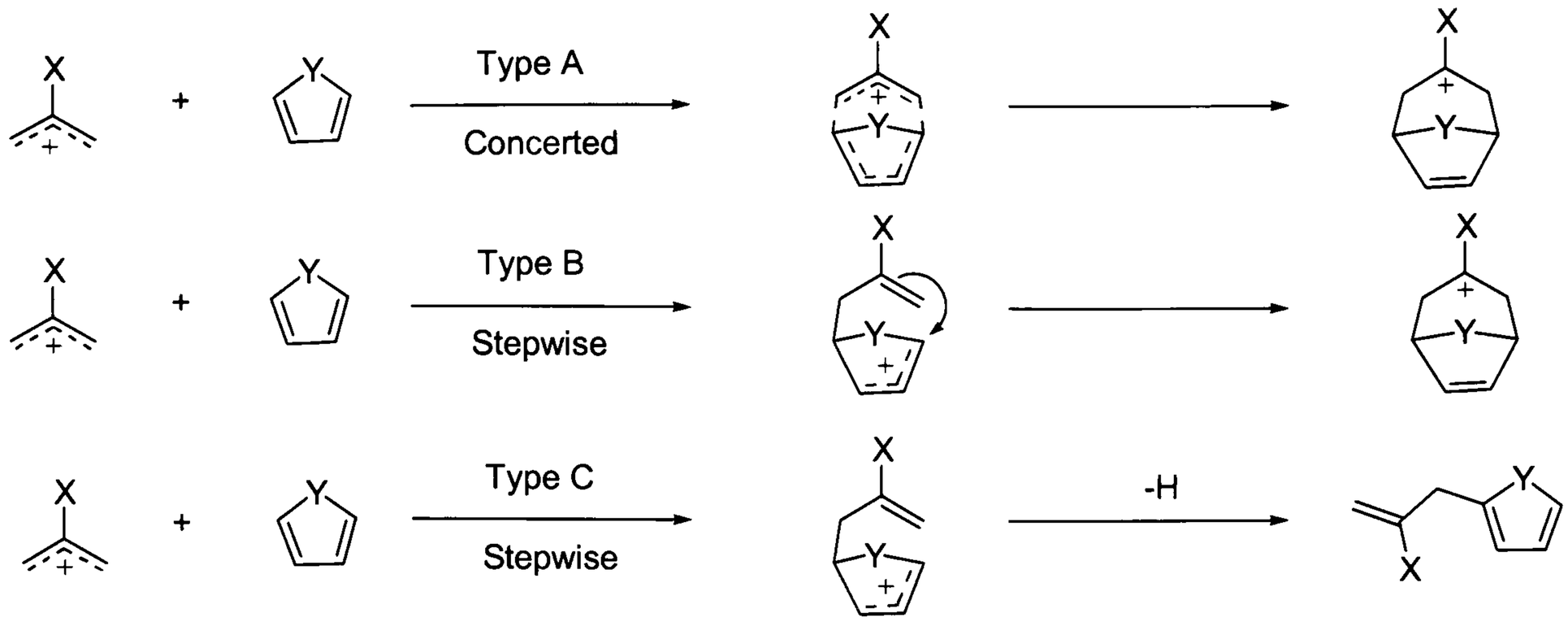


Scheme 11

There are two forms of [4 + 3] cycloaddition reactions, namely intermolecular and intramolecular. The intermolecular versions of the reaction has received much attention in recent years, though not as much as the closely related Diels-Alder reaction.

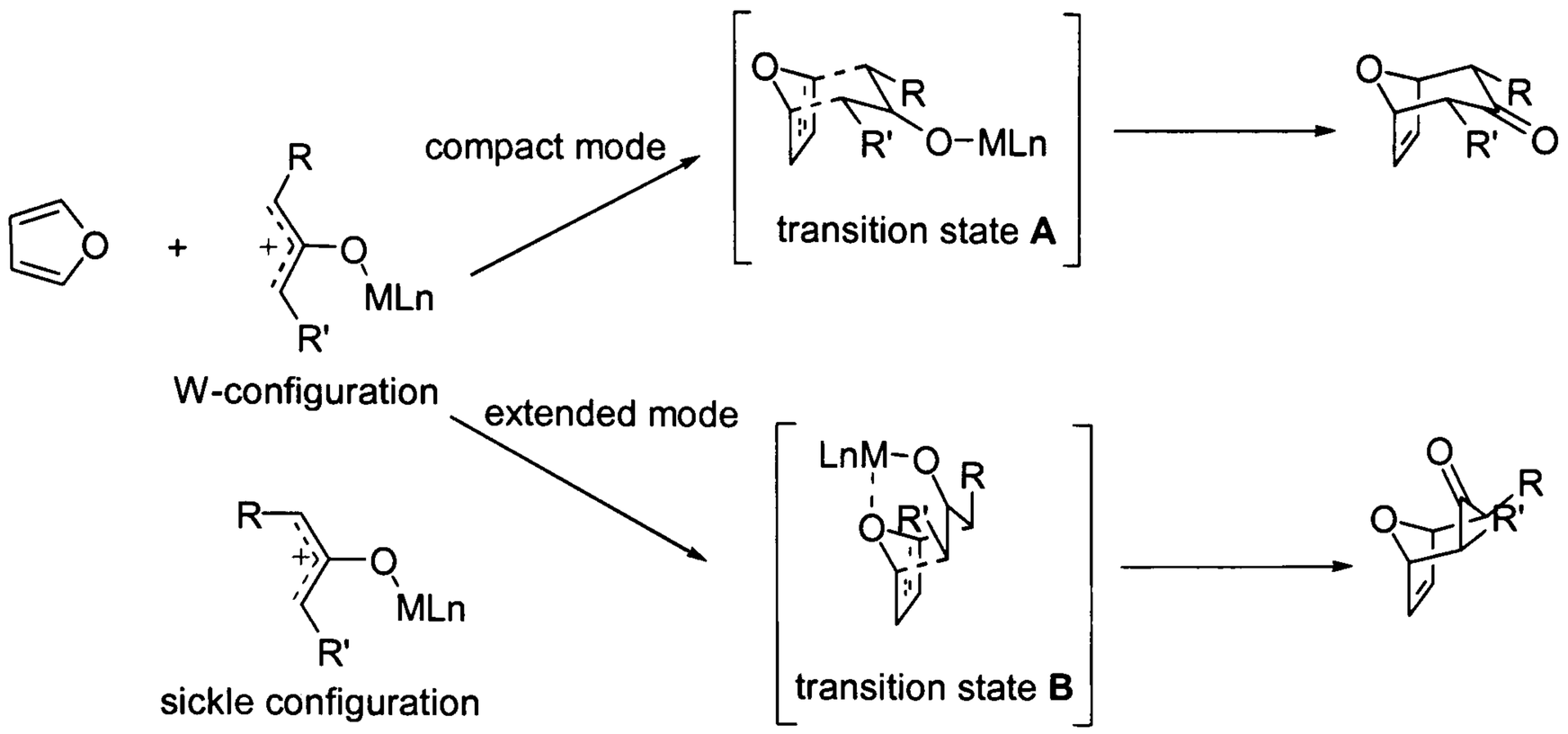
2.1.1 Intermolecular [4+3] Cycloadditions

The intermolecular [4+3] cycloaddition reactions of allyl cations with 1,3-dienes can be divided into three categories, namely type A, B and C, based on the mechanism and outcome.[34]



Scheme 12

Cycloadditions classified as type A are concerted (Scheme 12). The transition state of a type A cycloaddition is compact (a chair-shaped π interaction) or extended (a boat-shaped π interaction) and the configuration of the oxyallyl cation is retained (Scheme 13, X = Y = O).[64] Type B cycloadditions also leads to cycloadducts but through a stepwise mechanism (Scheme 12). The oxyallyl cation has a sickle configuration which may be retained or lost depending on the lifetime of the carbocation intermediate (Scheme 13). A type C reaction is where electrophilic addition occurs followed by loss of a proton (Scheme 12).



Scheme 13

2.1.2 Intramolecular [4+3] Cycloadditions

The intramolecular version of the [4+3] cycloaddition reaction is also divided into various types based on the connectivity between the allylic cation and the diene (Figure 4).

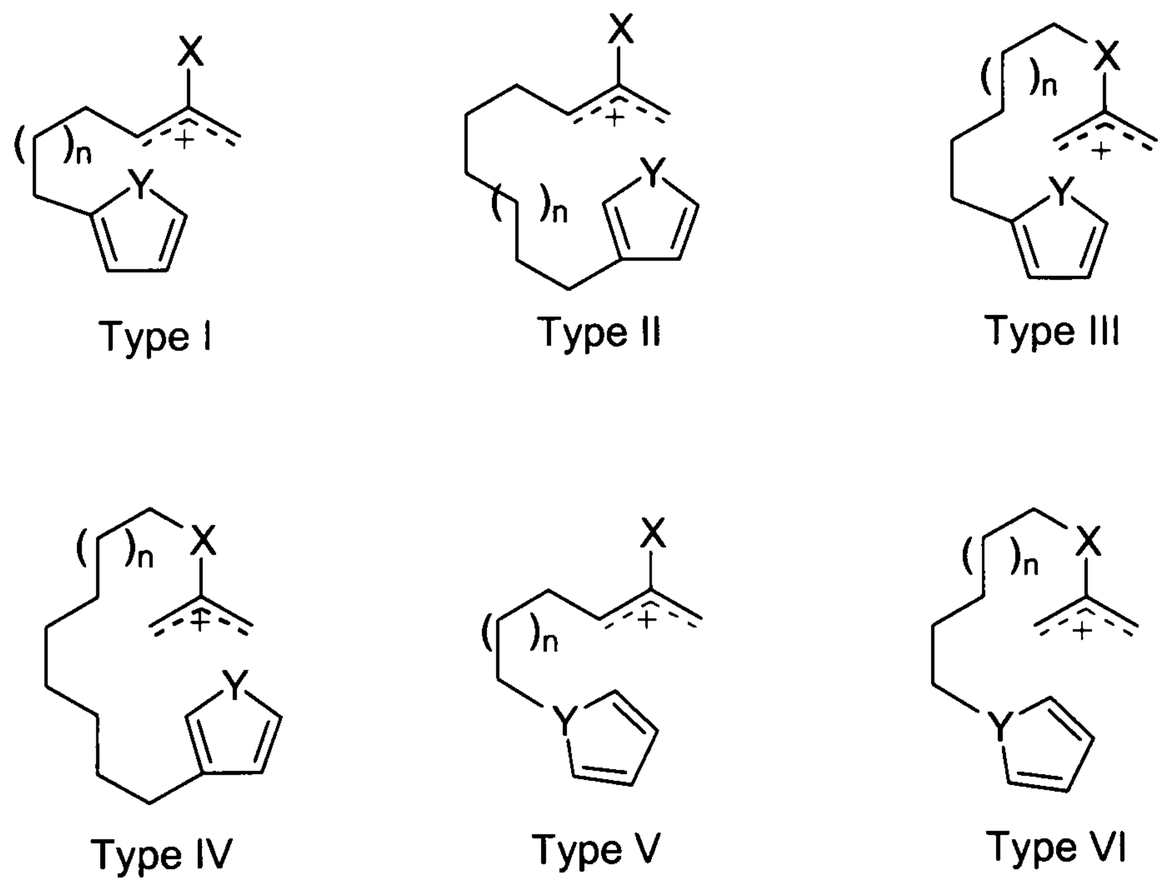
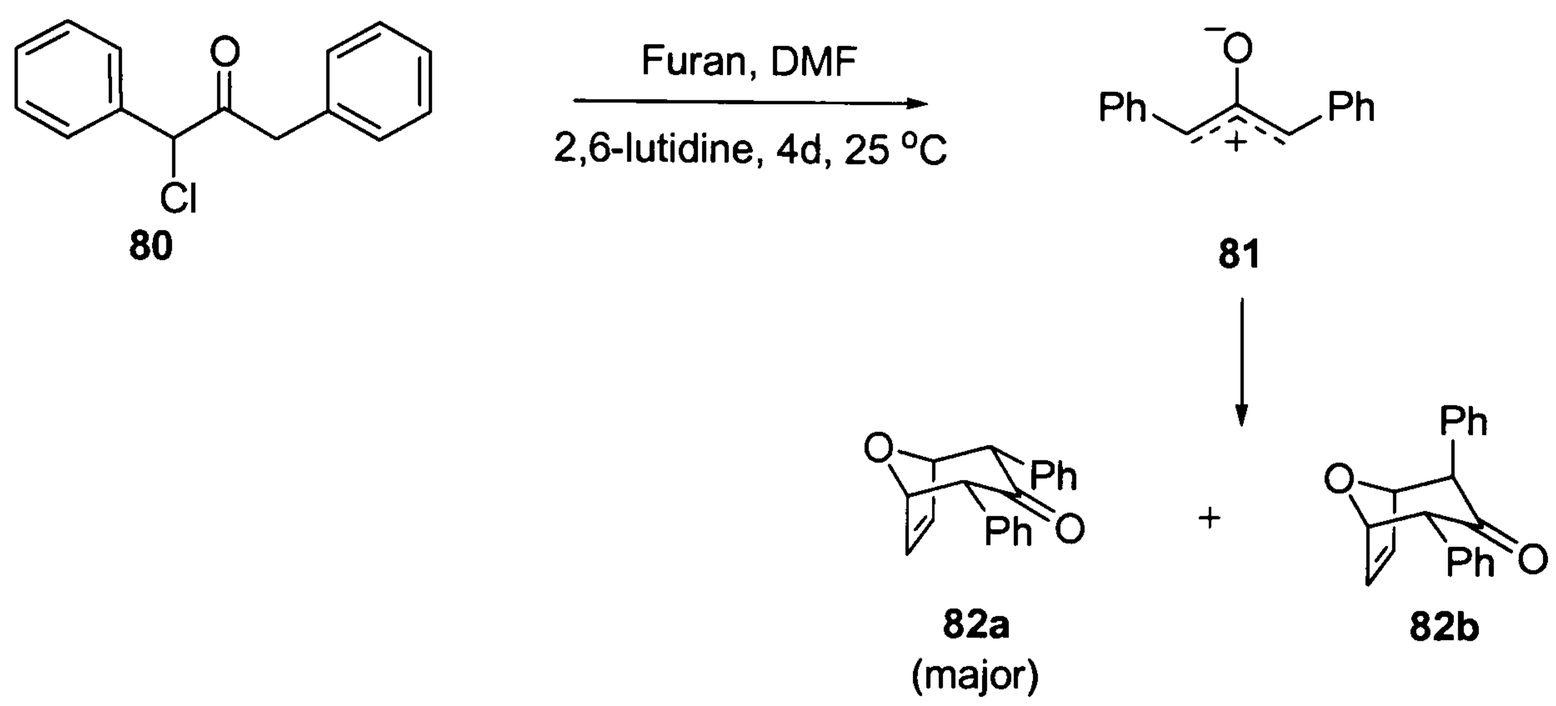


Figure 4

To date, only Type I intramolecular 4+3 cycloadditions have been reported in the literature.[35,36,37]

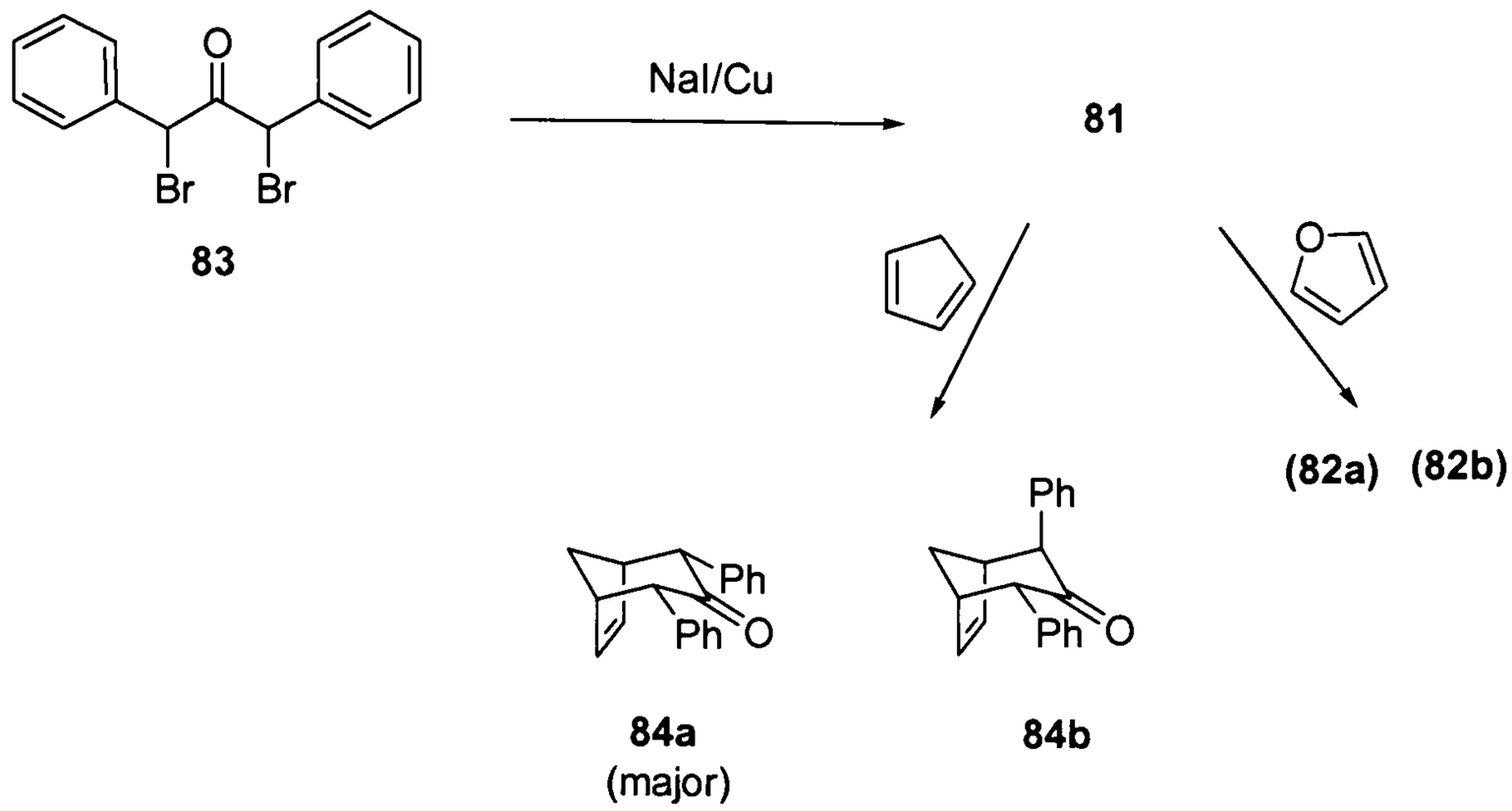
2.1.3 Generating the Oxyallyl Cation

The first evidence for the existence of oxyallyl cations was reported by Fort in 1962, when he treated chloro-dibenzyl ketone **80** with 2,6-lutidine in the presence of furan to yield cycloadducts **82a** and **82b** (Scheme 14). [38]



Scheme 14

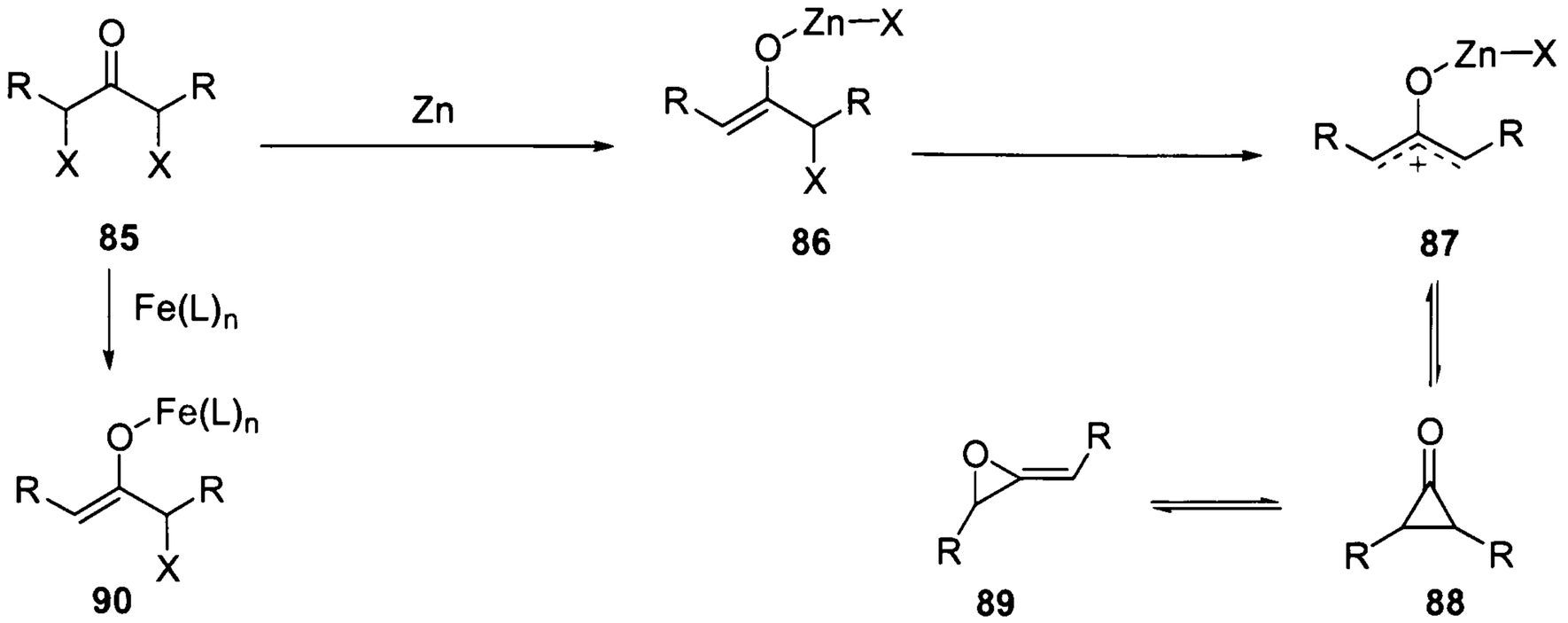
Cookson and co-workers also reported formation of **81** by treating dibromoketone **83** with sodium iodide, zinc-copper couple or mercury. Reaction of **81** with cyclopentadiene afforded the cycloadducts **84a** and **84b** (Scheme 15).[39]



Scheme 15

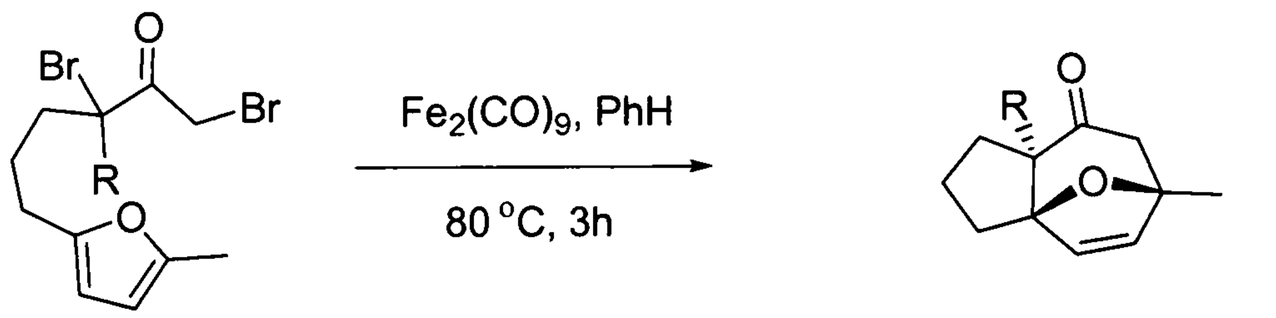
The stereochemical outcome in schemes 13 and 14 was rationalised by considering the geometry of the oxyallyl cation generated. Lautens postulated that the oxyallyl cation assumes the most stable W-configuration **81** (Scheme 14) and the cycloaddition occurs via the compact mode leading to the predominant cycloadducts **82a** and **84a** (scheme 15).[32] Cycloadducts **82b** and **84b** probably arise from the less stable sickle-configuration of the oxyallyl cation in a stepwise process.

Hoffmann and co-workers employed zinc to generate oxyallyl cation **87** (Scheme 16).[40] Theoretical calculations suggest that **87** is labile in the free form and therefore has the propensity to isomerise to **88** and **89** unless trapped by a suitable diene or solvent.[41] The oxyallyl cation **87** is stabilised by increasing the covalent character of the metal–oxygen bond or if the R substituents are electron-releasing (R = alkyl, aryl or halo).[42]



Scheme 16

Noyori employed diiron complexes in conjugation with dihaloketones to furnish oxyallyl cations such as **90** (Scheme 17).[43] For example, treatment of dibromoketone **91** or **92** with diiron nonacarbonyl in refluxing benzene gave **93** and **94** in 41% and 38% yields, respectively (Scheme 17). To date no other examples of intramolecular [4+3] cycloaddition reactions using this methodology have been reported. The lengthy route to the substrates, the lachrymatory nature of dibromoketones, as well as the use of toxic iron carbonyls are the major drawbacks to this methodology.



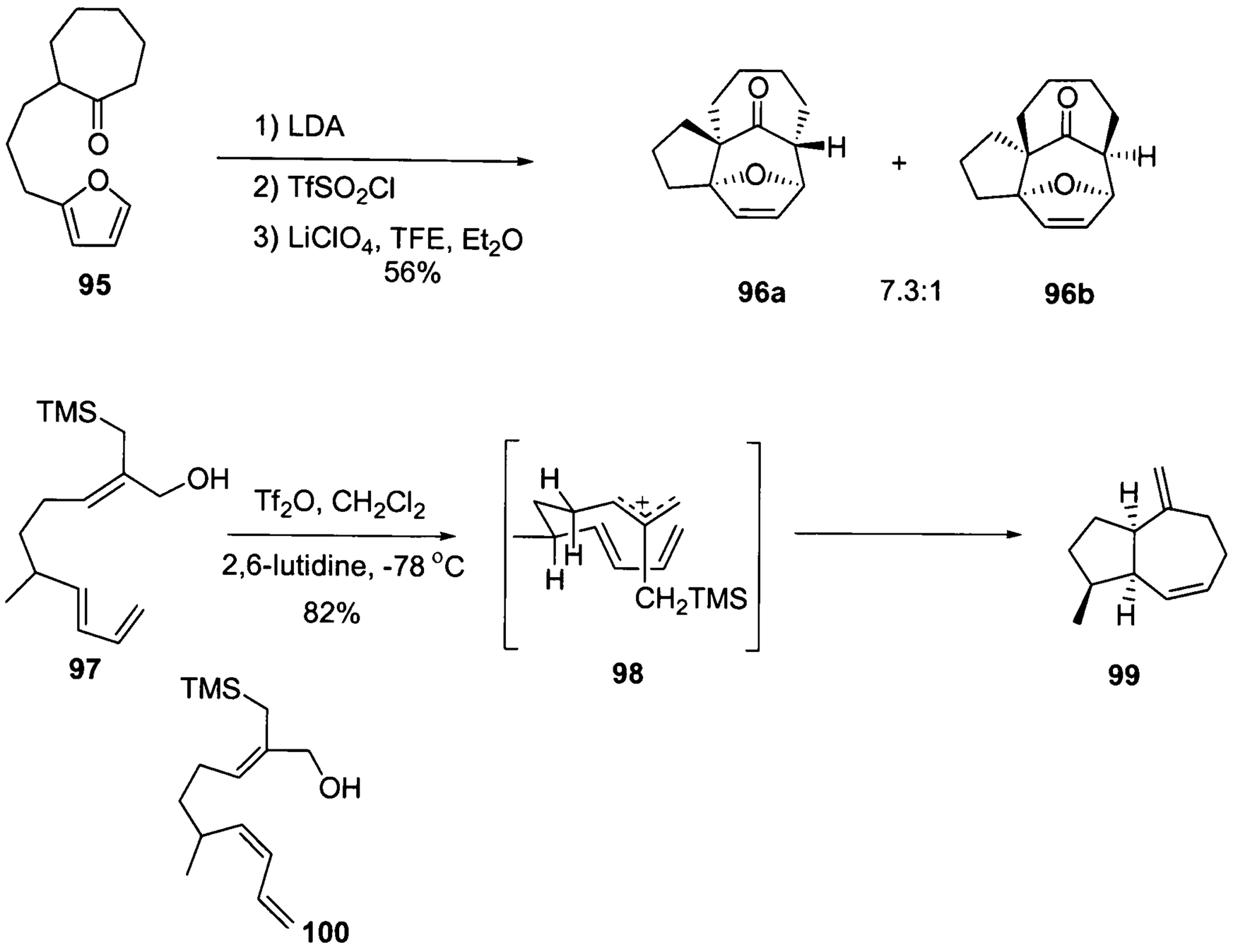
91, R = H
92, R = Me

93 R = H, 41%
94, R = Me, 38 %

Scheme 17

Enolate formation of ketone **95** followed by chlorination and a subsequent cyclisation under Föhlisch[44] conditions was reported by Harmata as a good method for the rapid assembly of the isoingenol skeleton (the cis ring junction of the ABC skeleton).[64]

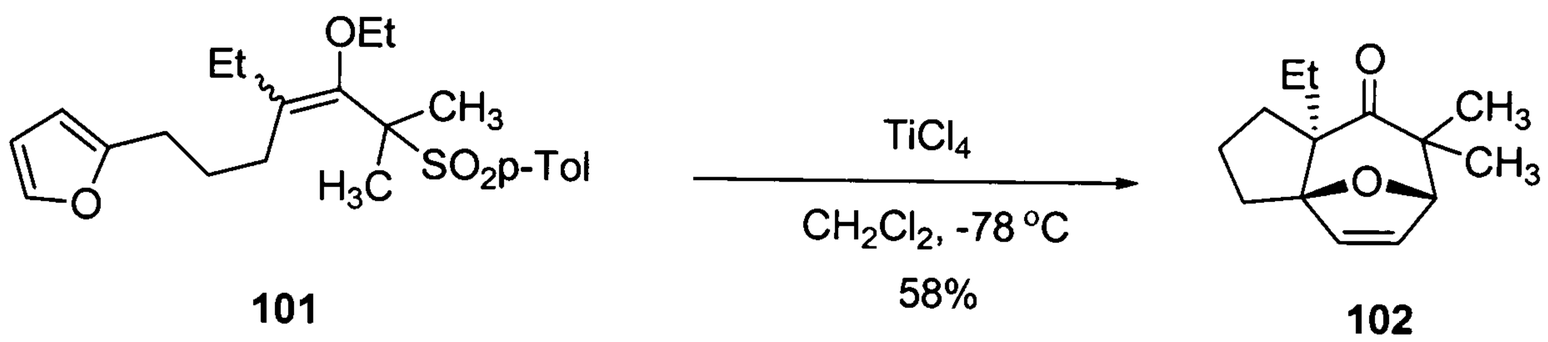
Cycloadduct **96** was isolated as a mixture of isomers in a 7.3:1 ratio (Scheme 18). Formation of the major cycloadduct **96a** was ascribed to an exo approach of the dienophile via an extended transition sate.



Scheme 18

Giguere[45] reported that the (oxy)-allylic cation configuration can have an effect on the course of the [4+3] cycloaddition. Treatment of alcohol (Z)-**97** with triflic anhydride gave **99** as the major adduct in 82% yield (Scheme 18). Formation of cycloadduct **99** was attributed to a concerted cycloaddition reaction and a conformational preference of allylic cation **98** which allows no interaction between the methyl and the bulky trimethylsilylmethyl substituents.[46] In contrast alcohol (Z)-**100** under same conditions as **97** gave no cycloadducts underlining the significance of the diene geometry (Scheme 18).[47]

Alkoxyallylic sulfones have also been used in [4+3] cycloaddition reactions. For example a mixture of (E) and (Z) sulfones **101** with titanium tetrachloride in dichloromethane at -78 °C gave **102** as the major product in 58% yield, suggesting that the stereochemical outcome of the reaction was independent of allylic cation stereochemistry. Isomerisation of the allylic cation was deemed possible under the reaction conditions (Scheme 19).[48]



101 **102**

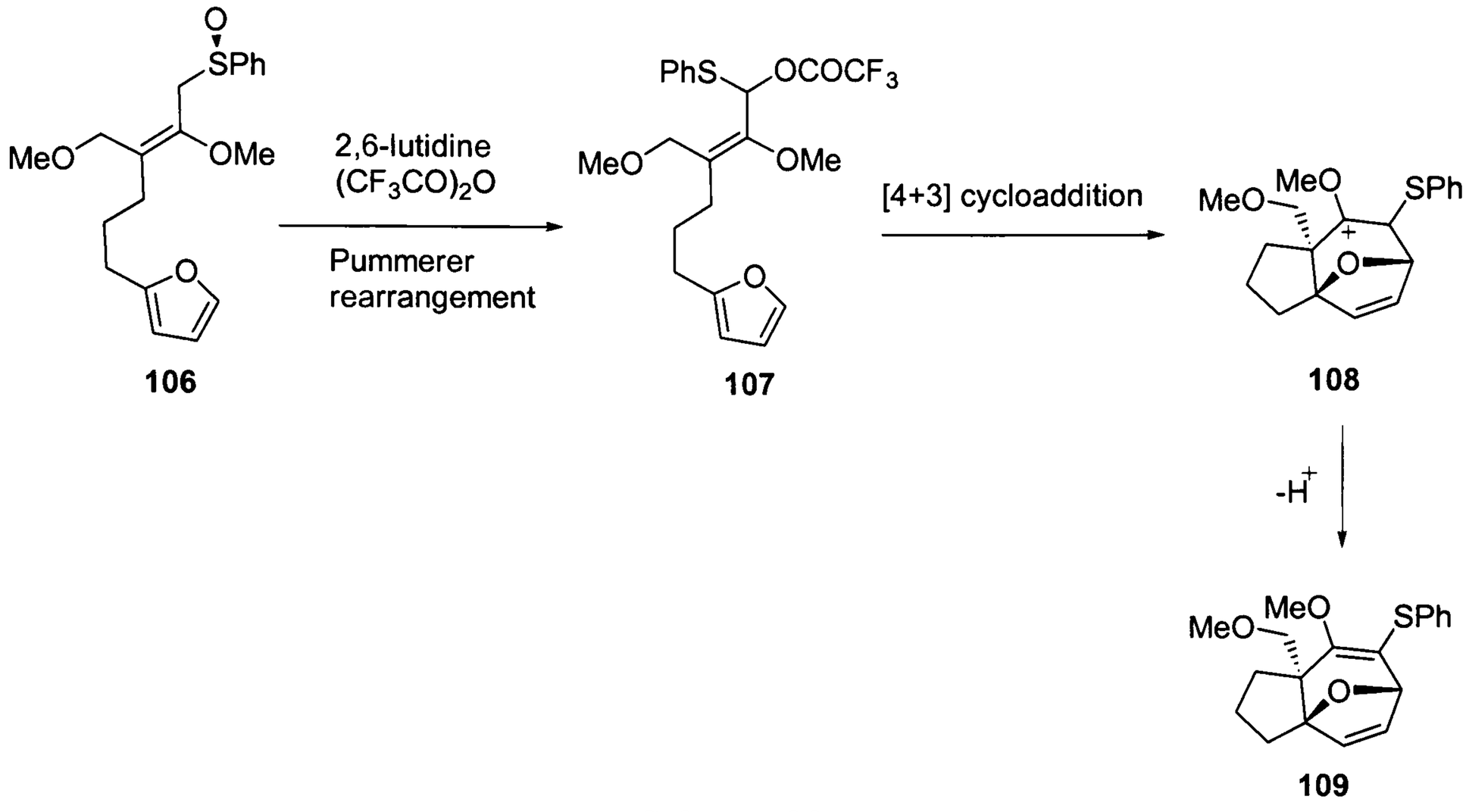
103 **104** 1:7.8 **105**

Scheme 19

Under photolytic conditions allylic sulfone **103** afforded cycloadducts **104** and **105**. The reaction was the first example of formation of allylic cation by photochemical activation which results in the transfer of electron to the sulfone functionality leading to an intermediate which ultimately ejects a sulfinate anion to produce the allylic cation (Scheme 19).[49]

Harmata and co-workers first reported allylic cations from sulfoxides.[50] For example, treatment of sulfoxide **106** with Tf_2O and 2,6-lutidine in dichloromethane underwent a

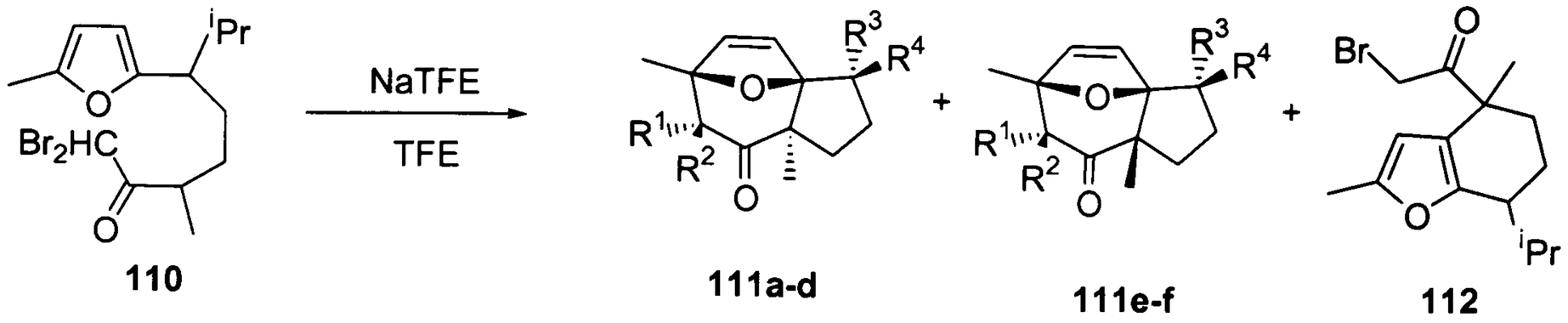
Pummerer rearrangement to form intermediate **107**.[51] An intramolecular [4+3] cycloaddition of the Pummerer intermediate **107** gave cycloadduct **108** which then lost a proton to afford the 5,7-fused cyclodduct **109** in 40% yield (Scheme 20).[52]



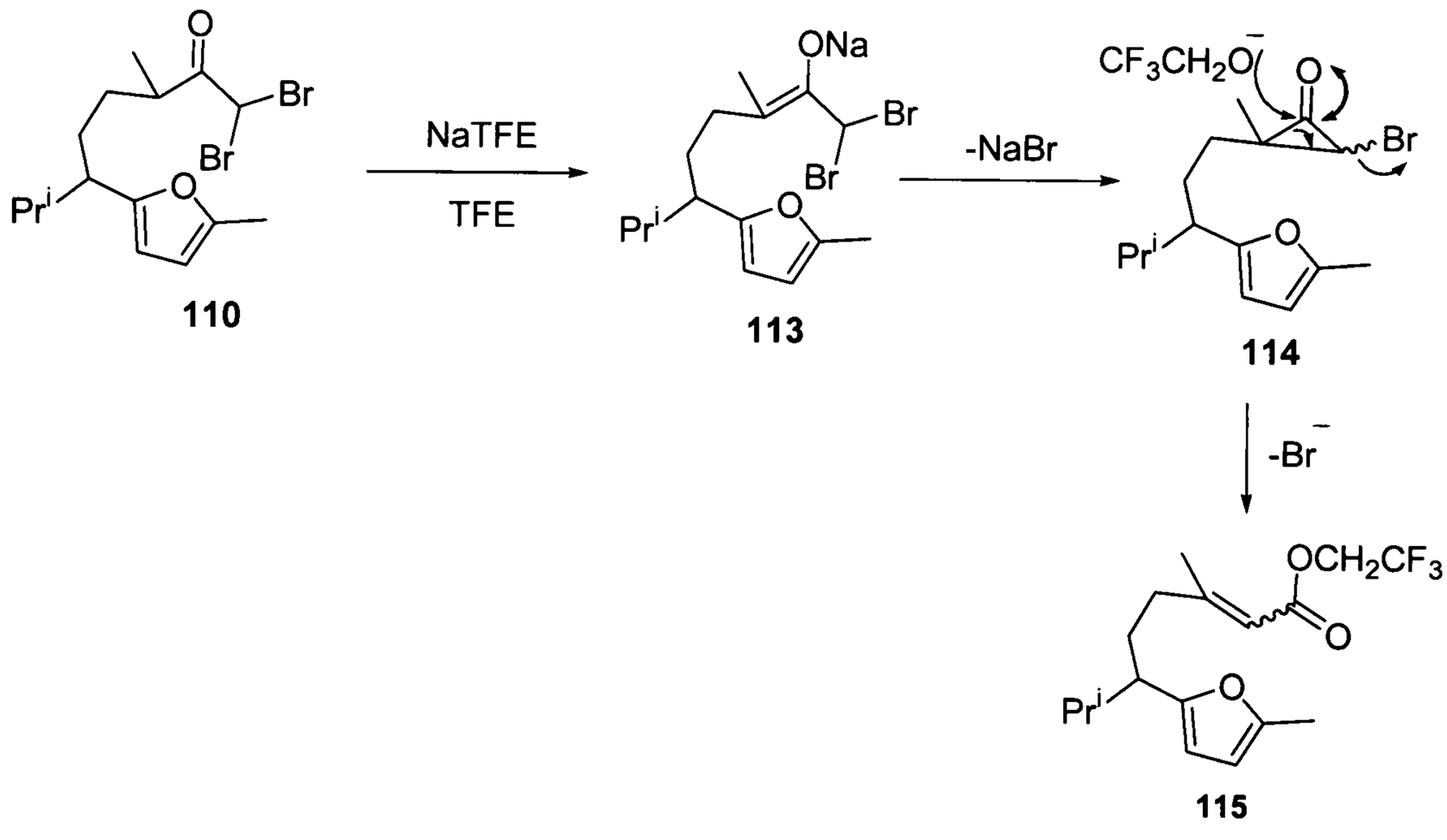
106 **107** **108** **109**

Scheme 20

Föhlisch and co-workers reported the use of sodium trifluoroethoxide (NaTFE) in trifluoroethanol (TFE) to generate allylic cations.[52] For example, dibromoketone **110** in a solution of NaTFE in trifluoroethanol (0.4 M) at room temperature for 6 days gave a mixture of six isomers **111a-f**, along with two diastereomeric furans **112** as by-products (Scheme 21).



product	R^1	R^2	R^3	R^4	yield(%)
111a	Br	H	H	^{i}Pr	31
111b	H	Br	H	^{i}Pr	9
111c	Br	H	^{i}Pr	H	14
111d	H	Br	^{i}Pr	H	3
111e	Br	H	H	^{i}Pr	25
111	Br	H	^{i}Pr	H	5
112					11



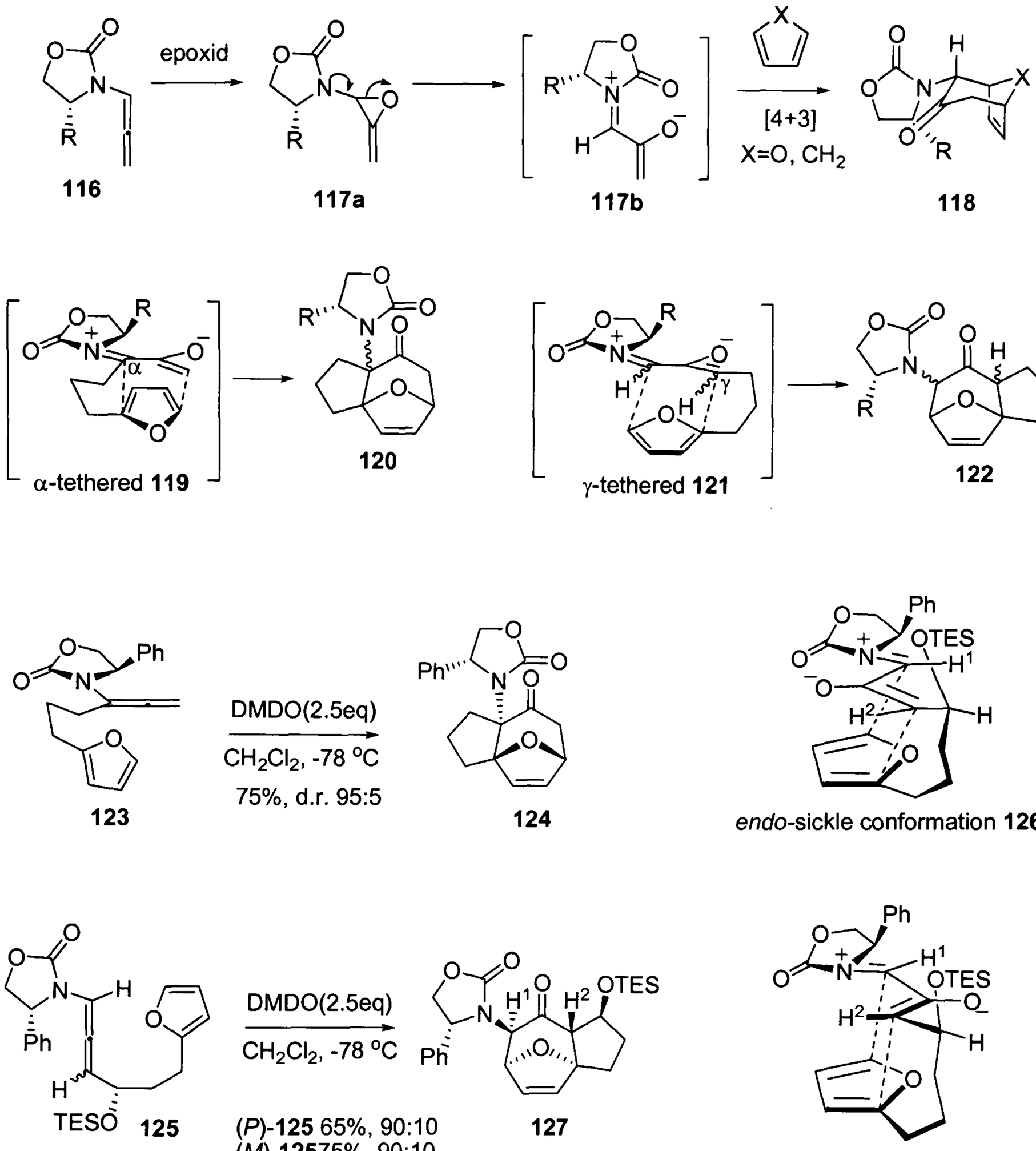
Scheme 21

In addition, two components with the possible molecular formula of $C_{17}H_{23}F_3O_3$ believed to be isomeric unsaturated esters of **115** were detected in traces (ca. 1% each) (Scheme 20). Formation of the esters was attributed to a possible Favorskii rearrangement of **110** with NaTFE (Scheme 21).[53,54,55]

Recently nitrogen-substituted oxyallyl cations have become the focus of attention in developing highly stereoselective [4+3] cycloaddition reactions.[56,57] Hsung[58] and co-workers first reported epoxidation of allenamides **116** to chiral oxyallyl cations **117a**, that can be made to participate in a highly stereoselective [4+3] cycloadditions with dienes to amides **118** (Scheme 22).

In the intramolecular variant of the reaction, the diene could be tethered to the allenamide at the α-position **119** or at the γ-position **121** to give cycloadducts **120** and **122** respectively (Scheme 22).[59] For example, epoxidation of α-tethered allenamide **123** (scheme 22) using 2.5 equivalent of dimethyldioxirane (DMDO) followed by stereoselective intramolecular [4+3] cycloaddition reaction gave cycloadduct **124** in 75% yield with distereomeric ratio of 95:5.[60] The stereochemical outcome of the reaction was attributed to an *endo* (or compact) cycloaddition and the preference of the oxyallyl cation **119** (Scheme 22, R=Ph) to adopt the most stable W configuration.[41,61]

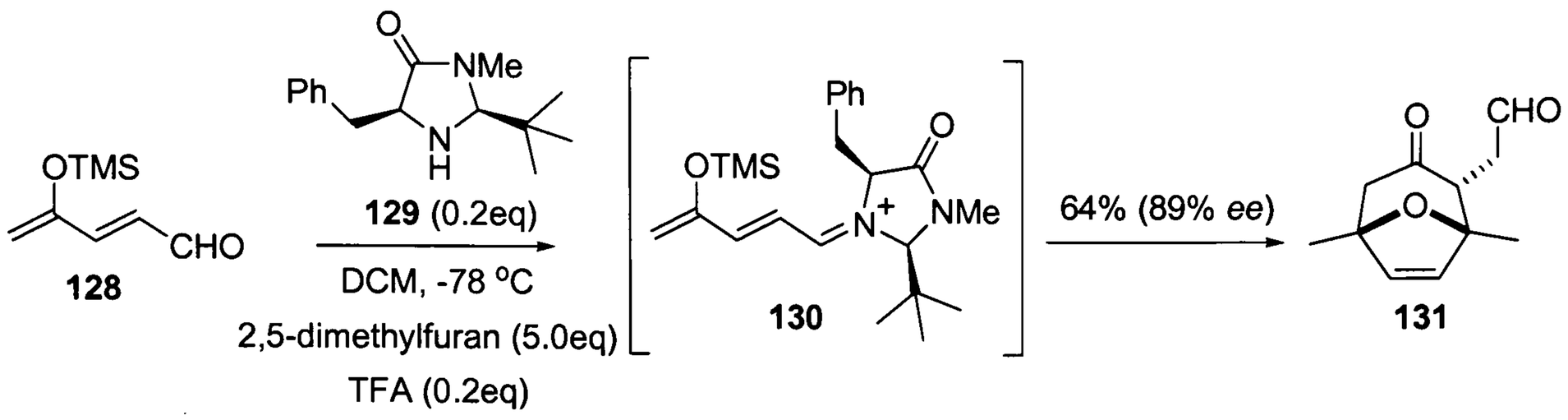
In contrast reaction of both γ-tethered allenamides (*P*)-**125** and (*M*)-**125** provided the same cycloadduct **127** in 65 and 75% yield respectively, in 90:10 ratio indicating that the chirality of the allene has no influence on the stereoselective outcome of the reaction (Scheme 22). Since H^1 and H^2 in **127** may be assigned as *anti*, formation of **127** was attributed to the oxyallyl cation adopting sickle conformation **126a** through an *endo* addition or sickle conformation **126b** through an *exo* addition (Scheme 22).[61]



Scheme 22

Harmata[62] reported an example of asymmetric organocatalysis in [4+3] cycloaddition reactions with furan. For example, addition of *in situ* generated chiral iminium ion **130** to 2,5-dimethylfuran resulted in the formation of keto aldehyde **131** in 64% yield and 89% *ee* with the liberation of amine **129** which could participate in further reaction cycles (Scheme 23). The stereochemical out come of the reaction was attributed to a

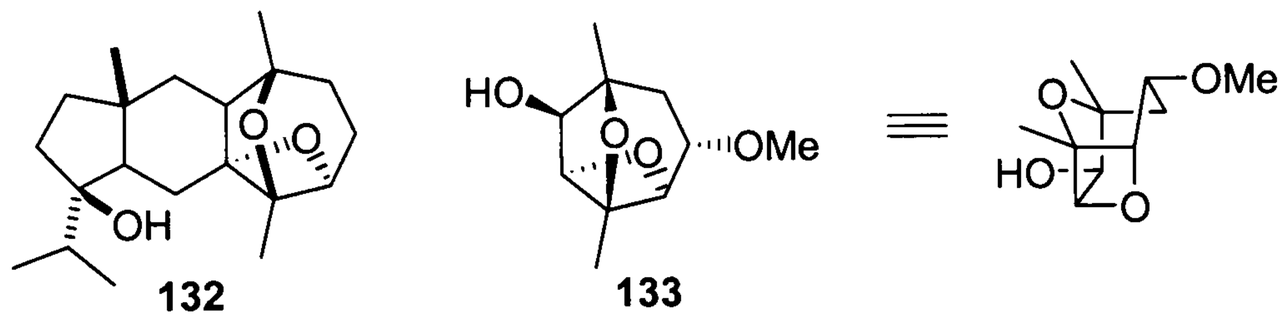
compact transition state and face selectivity dictated by iminium ion **130**, although the absolute configuration of **131** has yet to be determined (Scheme 23).[63]



Scheme 23

2.1.4 Summary

In conclusion, the [4+3] cycloaddition reaction of allylic cations and dienes is synthetically a powerful method for producing complex and interesting seven-membered ring systems. In particular, the methodology has shown to be broadly applicable to the synthesis of oxabicyclic systems under a number of conditions. The concept of asymmetric [4+3] cycloadditions first introduced by Kende and Huang[64] is intellectually appealing and is applicable to key polycyclic ring systems identified in some natural products. An example is the asymmetric synthesis of **133** corresponding to the 2,7-dioxatricyclo [4.2.1.$0^{3,8}$] core of the marine metabolite dictyoxetane **132** (Scheme 24).[65]

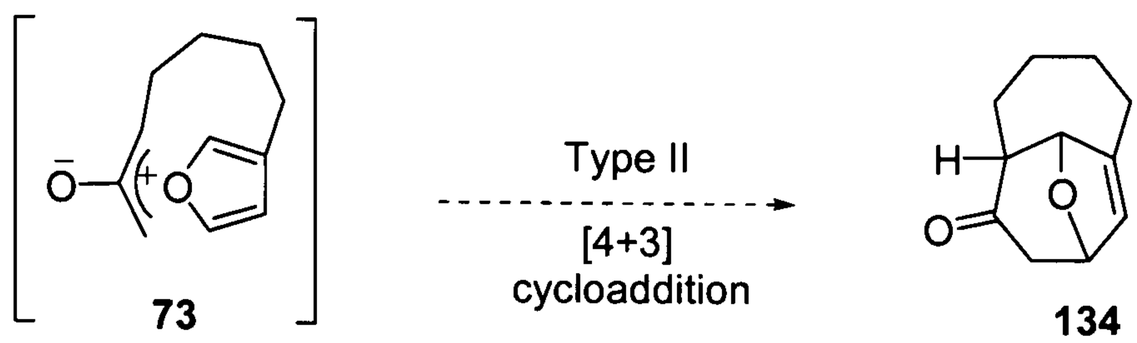


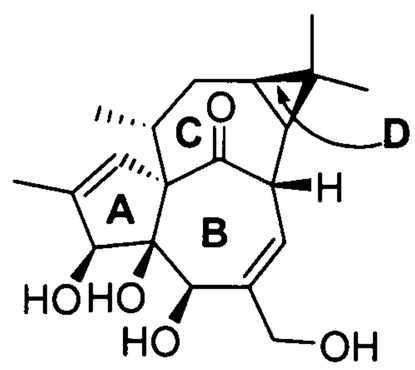
Scheme 24

However, mechanistic studies and methodological development remain areas of the reaction where further development is required. Furthermore, the Type-II, III, IV, V and VI are all areas of the reaction that are yet to be investigated. Thus, any contribution in these arenas will widen the scope of the reaction and bring synthetic target of high complexity within reach.

2.2.0 Results and Discussion I-Towards the BC- ring of ingenol

The initial aim of the project was to investigate a Type-II intramolecular [4 + 3] cycloaddition reaction of an oxyallyl cation tethered to the 3-position of a furan as a means to construct the [4.4.1] bicyclic skeleton (BC ring system) of the natural product ingenol (Scheme 25).[66]





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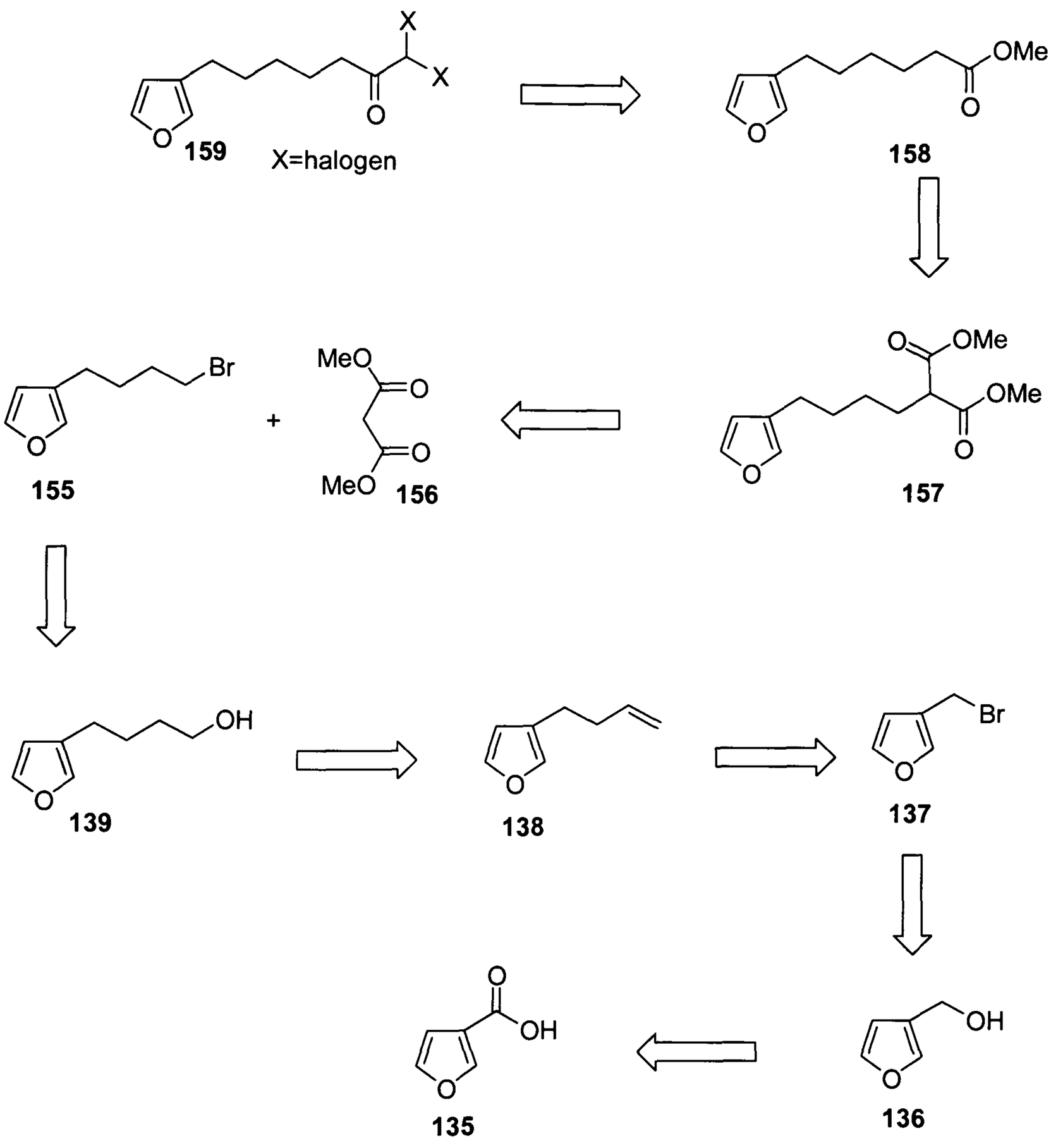
Scheme 25

Although there are a variety of precursors that can be used to generate oxyallyl cations, α-haloketones have found most application in the chemical literature.[32,34,37,67] To that end, α-dihaloketones **159** (Scheme 26) were deemed suitable precursors to oxyallyl cation **73** (Scheme 25). A retrosynthetic analysis of **159** required to test the proposed Type II [4+3] cycloaddition reaction is outlined in Scheme 26. It was anticipated that required dihaloketones **159** may be prepared from alkylation of carboxylic acid ester **158**. Ester **158** can be obtained by decarboxylation of diester **157**. The reaction between commercially available dimethylmalonate **156** and bromide **155** should afford diester **157**. Bromide **155** may be prepared from bromination of alcohol **139**. The known alcohol **139** can be prepared by hydroboration of alkene **138**,

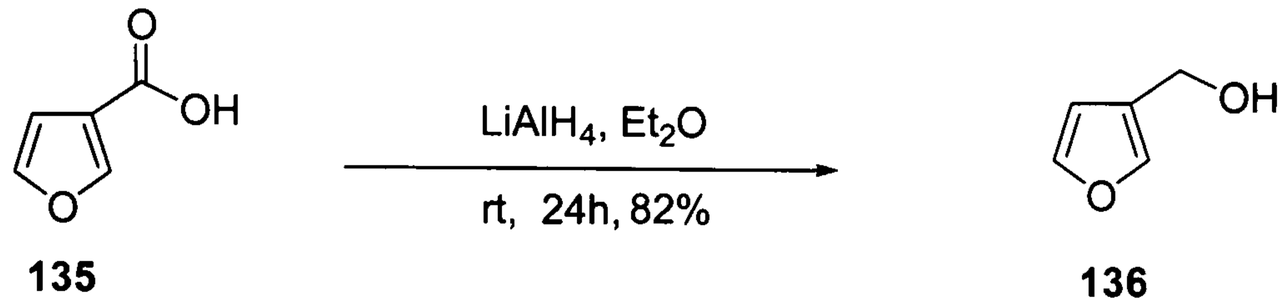
which in turn is prepared from the reaction of bromide **137** and a suitable Grignard reagent. Bromide **137** can be prepared from bromination of alcohol **136**. Reduction of commercially available 3-furoic acid **135** should bring in hand alcohol **136** (Scheme 26).



Scheme 26

Reduction of commercially available furoic acid **135** with 1.2 equivalents of lithium aluminium hydride in sodium dried diethyl ether afforded the desired alcohol **136** in

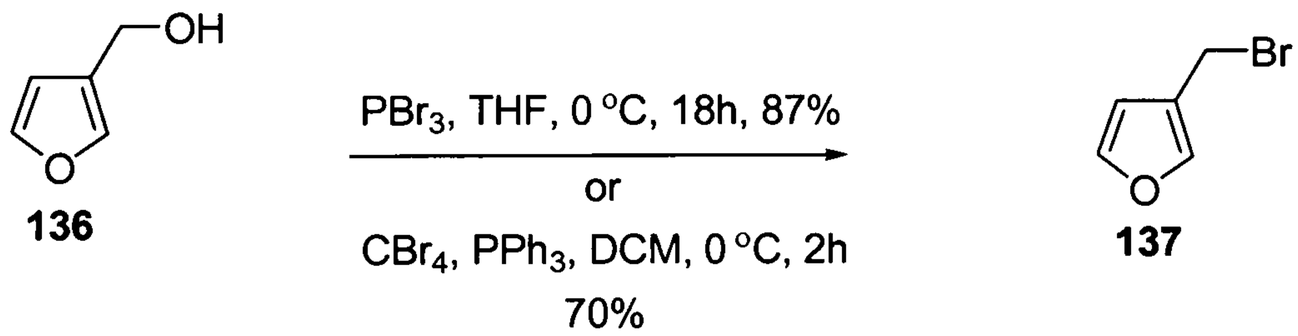
excellent yield 82% (lit.[68], 91%). Alcohol **136** was purified by a short path distillation using a Kugelrohr apparatus (2 mm/Hg, b.p. 65-70 °C) (Scheme 27).



135 **136**

Scheme 27

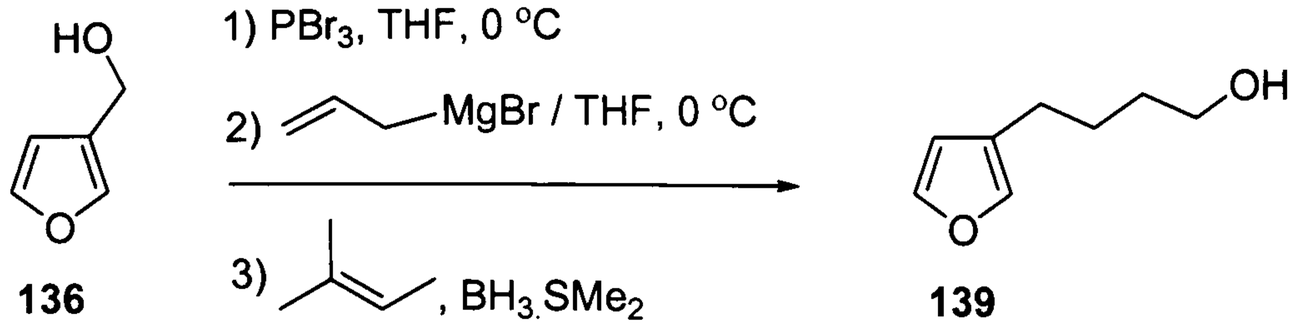
Direct bromination of alcohol **136** using phosphorus tribromide gave the desired bromide **137** without incident.[69] Bromide **137** was also obtained from a reaction between **136** and carbon tetrabromide in the presence of triphenylphosphine (Scheme 28).[68] Removal of the triphenylphosphine oxide by-product proved problematic, owing to its propensity to stay in solution. Nonetheless, the latter methodology was the preferred synthetic route to **137** due to faster reaction time and cheaper reagents.



136 **137**

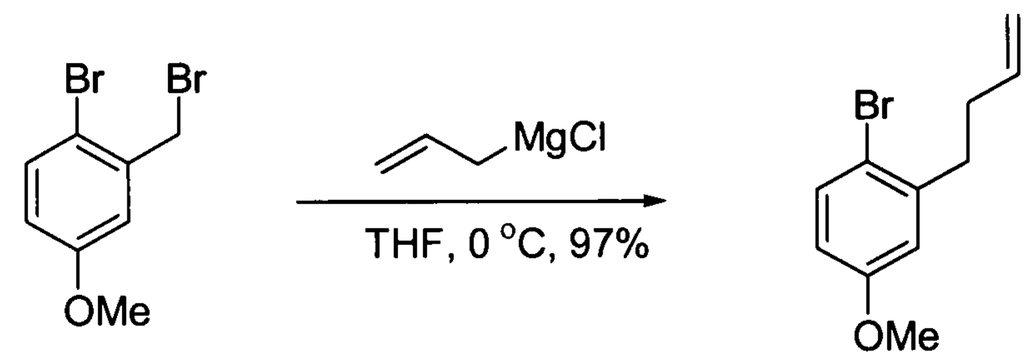
Scheme 28

A "one-pot" synthetic route to alcohol **139** in accordance to the literature involves conversion of alcohol **136** to bromide **137**, which in turn was converted to alkene **138**. Hydroboration of alkene **138** afforded only 20% of alcohol **139** (lit.[69] 49%) over three steps (Scheme 29).



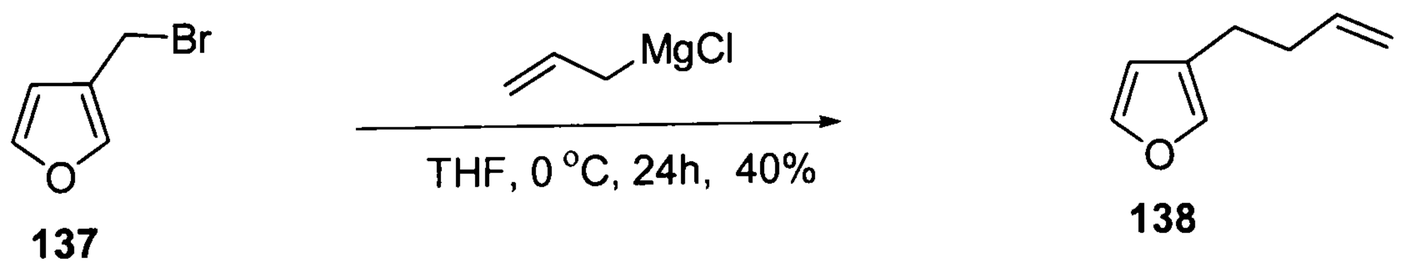
Scheme 29

Taber and Malcom reported formation of alkene **141** from alkylation of dibromide **141** using freshly prepared allylmagnesium chloride in THF (Scheme 30).[70]



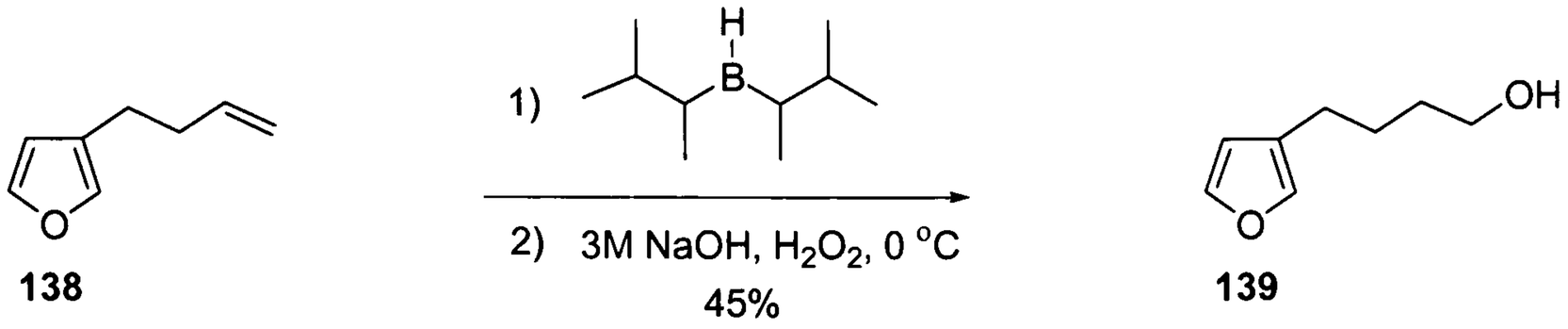
Scheme 30

In an attempt to improve the yield of alcohol **139**, Taber and Malcom's methodology was first tried on substrate **137**. Allylation of bromide **137** using allylmagnesium chloride furnished alkene **138** in satisfactory yield. The crude product was sufficiently pure to be used in the next step without further purification. (Scheme 31).[70]



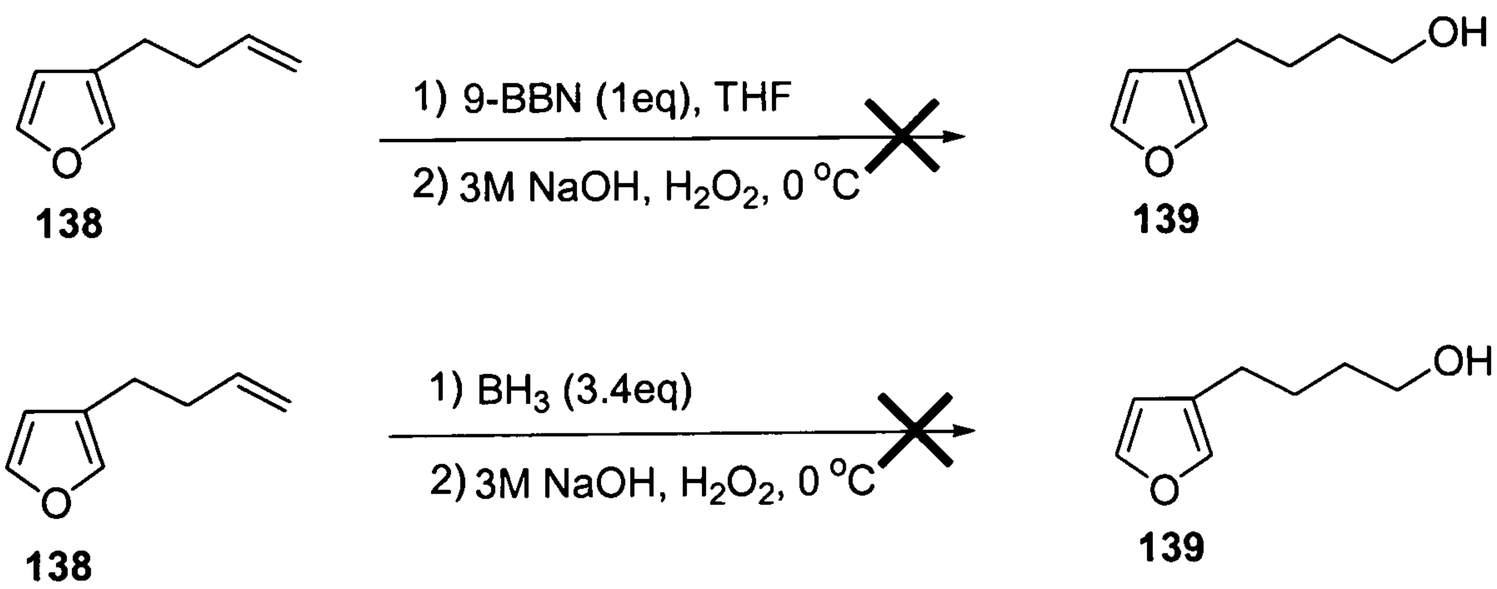
Scheme 31

Conversion of freshly prepared olefin **138** to desired alcohol **139** was effected by selective hydroboration of the double bond using a freshly prepared solution of disiamylborane. This was followed by hydrolysis using 3M NaOH and 27% H_2O_2 to afford the homologated alcohol **139** in 45% yield (Scheme 32).[69]



Scheme 32

Attempted conversion of **138** to **139** using commercially available 9-BBN and BH_3 failed to deliver any of desired alcohol **139** (Scheme 33), although the reactions were attempted only once and on small scale.

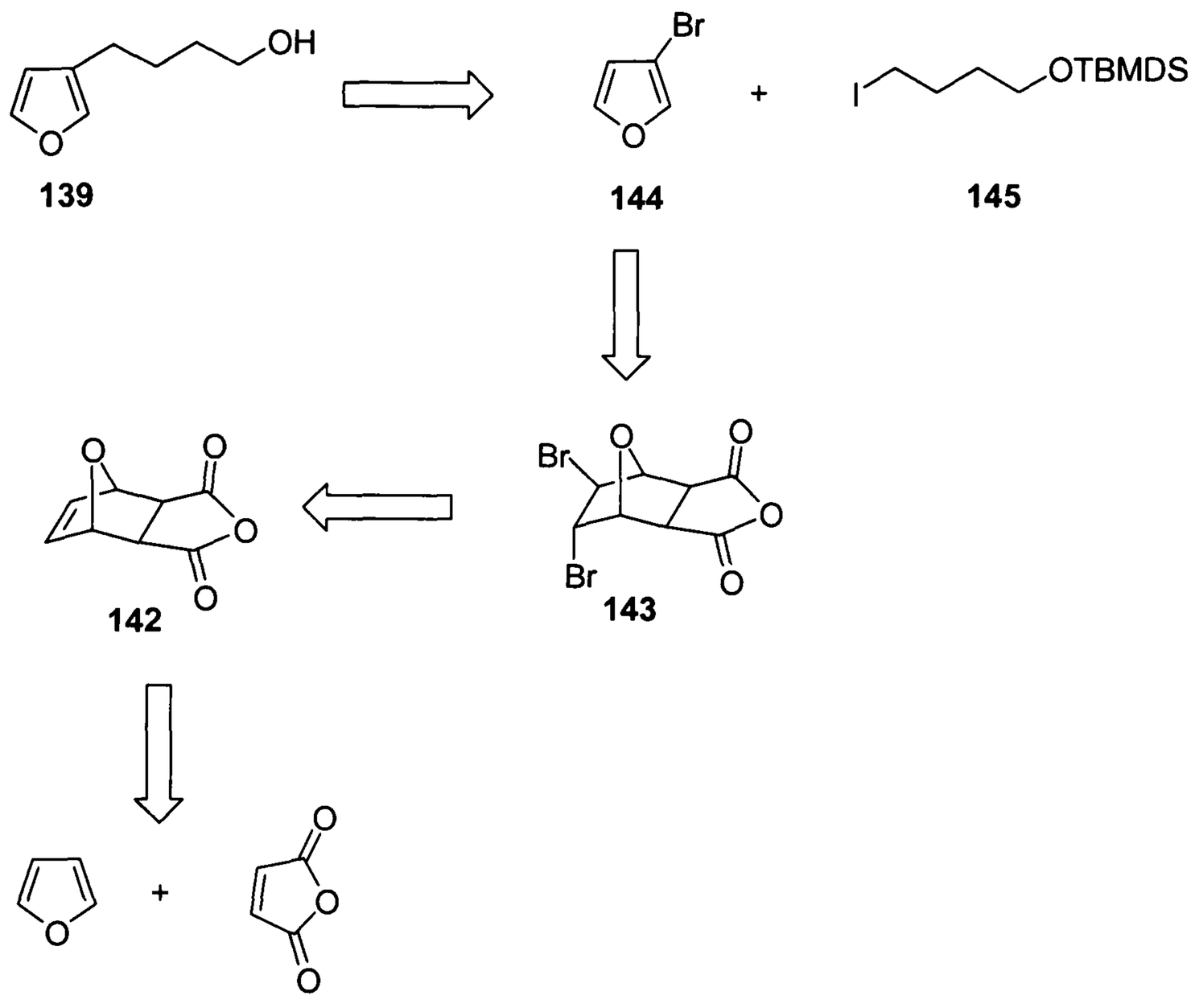


Scheme 33

In an attempt to improve the overall yield of alcohol **139**, an alternative synthetic route was explored (Scheme 34).

It was anticipated that alcohol **139** may be prepared from a cross coupling reaction between 3-bromofuran **144** and iodide **145** followed by deprotection (Scheme 34).

The reaction between tetrahydrofuran, sodium iodide and *tert*-butyldimethylsilyl chloride should furnish iodide **145**. Bromide **144** may be formed from a simultaneous dehydrobromination and retro Diels-Alder reaction of adduct **143**. Bromination of adduct **142** should give the *trans* dibromide **143**. A Diels-Alder reaction between furan and maleic anhydride should furnish adduct **142** (Scheme 34).

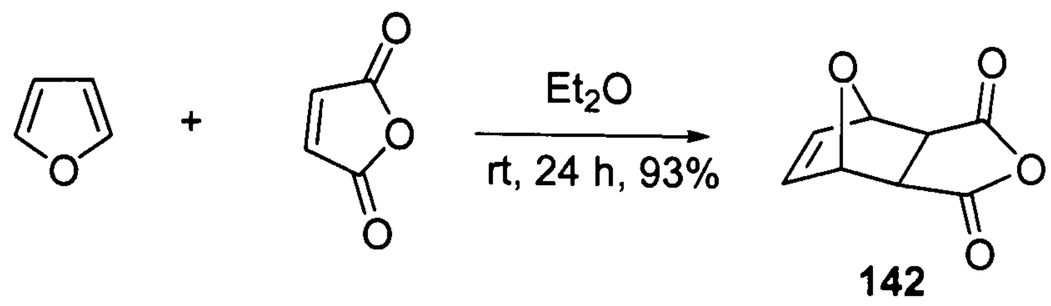


139 **144** **145**

142 **143**

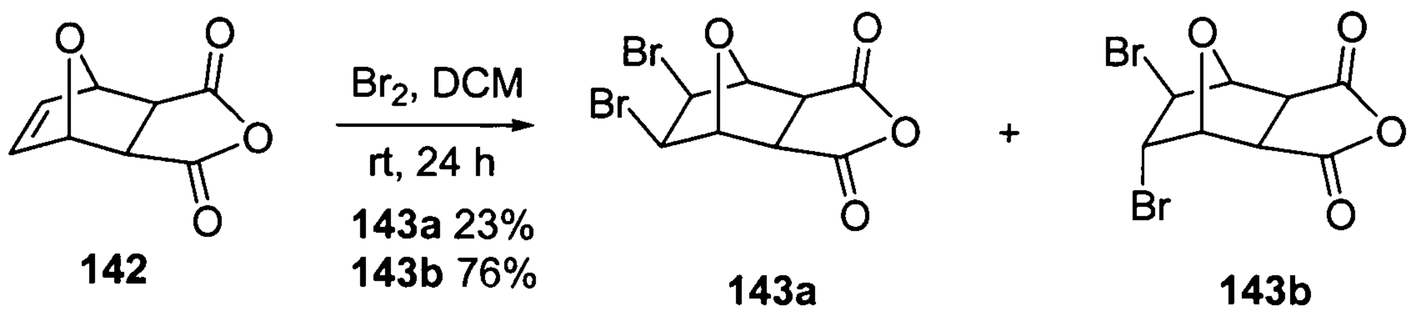
Scheme 34

The Diels-Alder reaction between furan and maleic anhydride proceeded smoothly at room temperature to give the thermodynamically more stable adduct **142** as a solid in 93% yield (Scheme 35).[71]



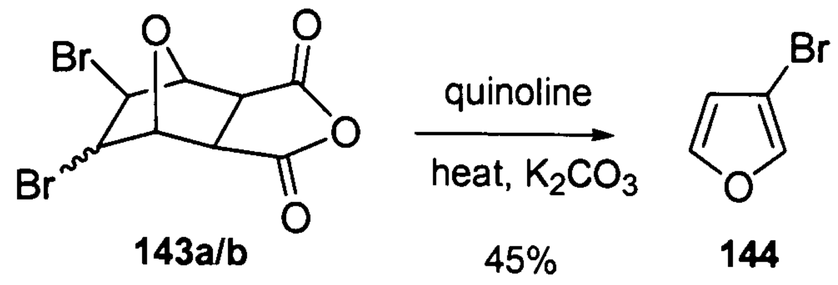
Scheme 35

The reaction between bromine and adduct **142** in dichloromethane at room temperature gave a mixture of diastereomers **143a** and **143b** (Scheme 36). Separation of the diastereomers was easily accomplished since the higher melting point (328-330 °C) product **143a** was not soluble in the reaction solvent and could easily be separated by filtration. Concentration of the mother liquor *in vacuo* gave the lower melting point (156-158 °C) product **143b** (Scheme 36).[72]



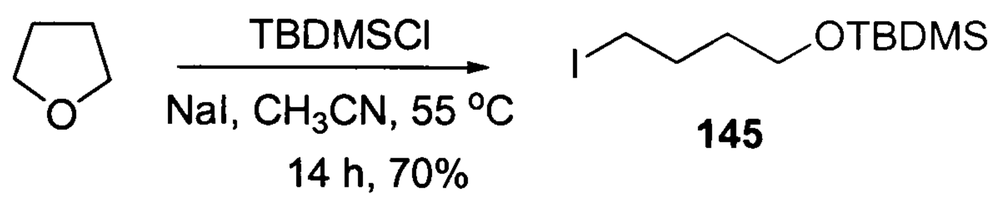
Scheme 36

A retro-Diels-Alder reaction of a mixture of brominated adducts **143a/b** in quinoline was effected by slowly heating the mixture up to 220 to 230 °C. Crude product was collected at this temperature and dried over sodium sulphate. The crude distillate was purified by a second distillation through a column to give 20% of bromide **144** (lit. 60%).[73] The yield of bromide **144** was unacceptable; as a result, the literature procedure was slightly modified. It was pleasing to observe that re-distillation of the crude reaction from potassium carbonate improved the reaction yield to 45% (Scheme 37).



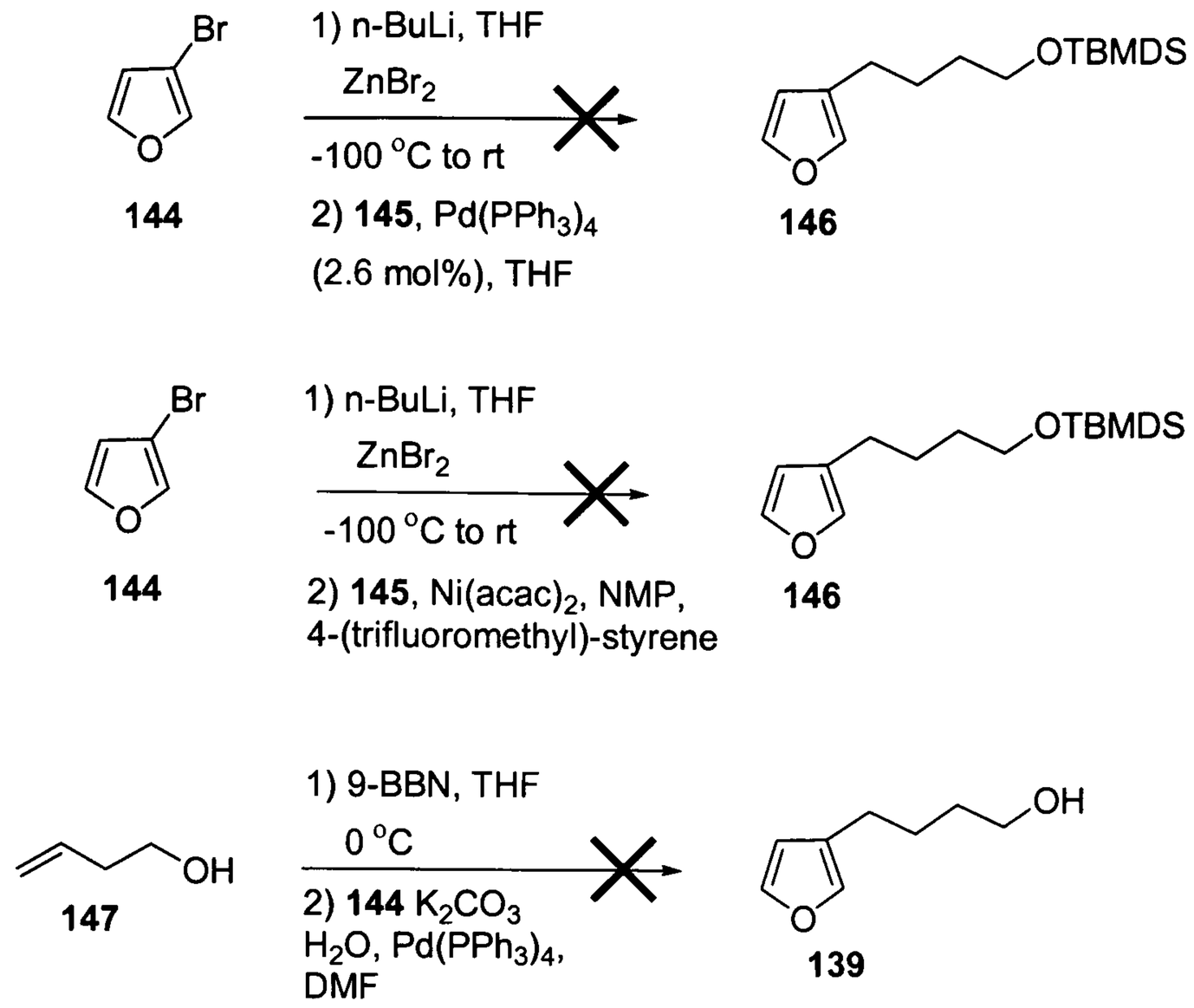
Scheme 37

Formation of iodide **145** was effected by heating tetrahydrofuran and *tert*-butyldimethylsilyl chloride in the presence of sodium iodide at 55 °C in acetonitrile (Scheme 38).[74] The crude product was sufficiently pure to be used in the next step without further purification.



Scheme 38

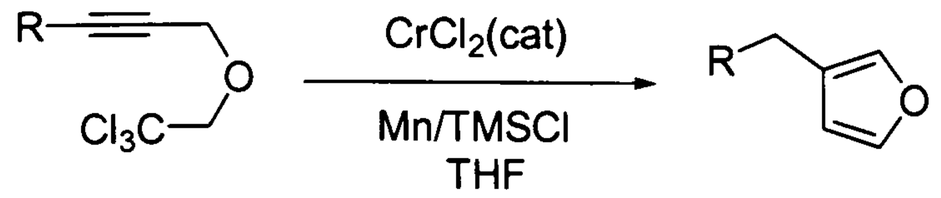
With bromide **144** (Scheme 37) and iodide **145** (Scheme 38) in hand, a metal mediated cross coupling reaction between bromide **144** and iodide **145** was attempted. It was disappointing to note that both Pd[75,76] and Ni[77] mediated reaction between **144** and **145** failed to deliver any of the desired cross-coupled product **146** (Scheme 39). A possible reason for the reaction failure may be that sequential treatment of **144** with *n*-BuLi and $ZnBr_2$ did not produce any organozinc derivative although, lithium - bromine exchange on 3-bromofuran is well documented.[78]



Scheme 39

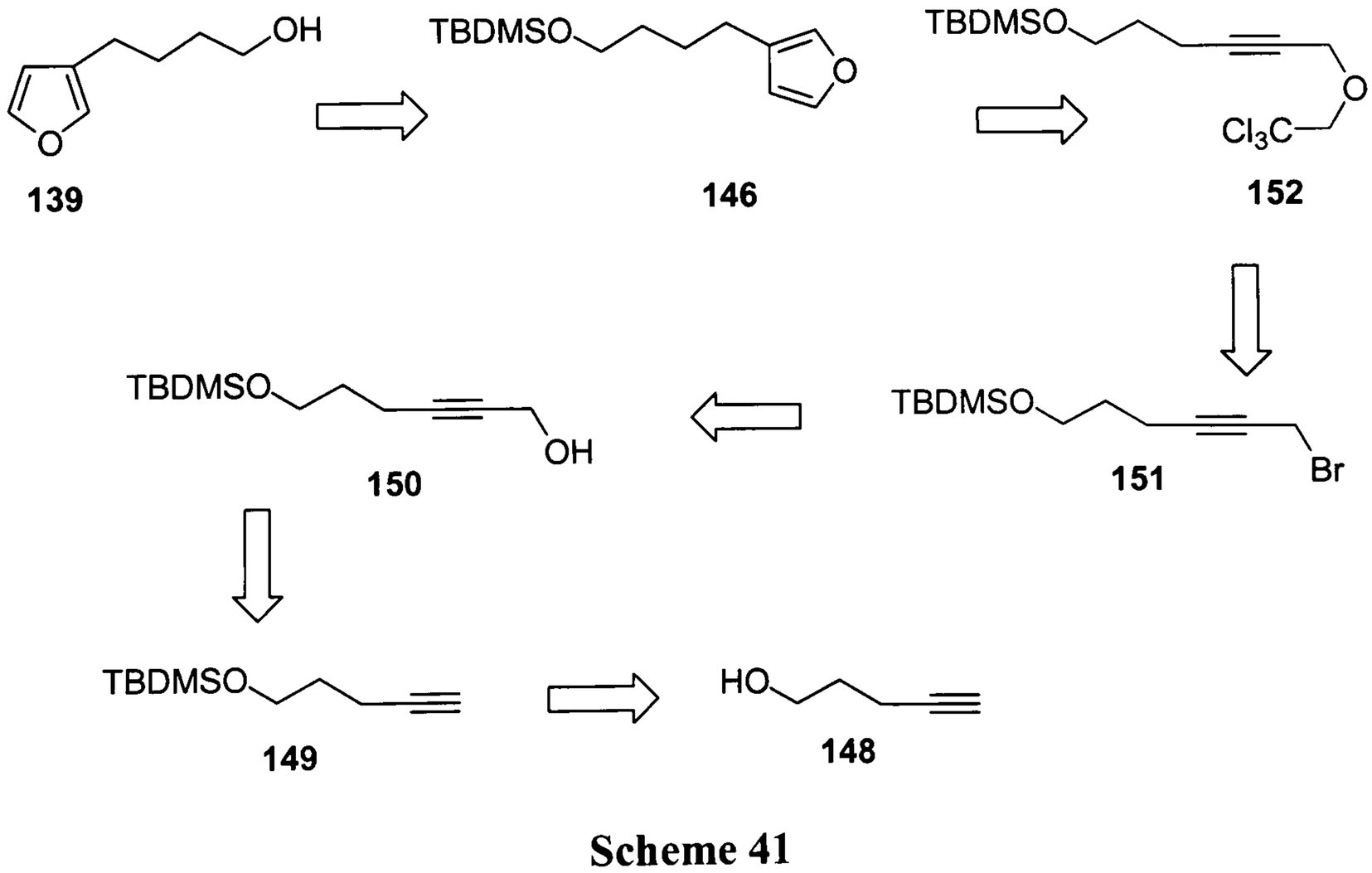
Attempted cross coupling reaction between alcohol **147** and bromide **144** using Suzuki's[79] protocol for hydroboration of alkenes, followed by coupling of the *B*-alkyl-9-borabicyclo[3.3.1]nonane derivatives with aryl bromides yielded none of the desired alocohol **139** (Scheme 39). Hydrolysis of the crude reaction using 3M NaOH and 27% H_2O_2 afforded 1,5-dihydroxy butane resulting from hydroboration of alcohol **147** pointing to the reluctance of bromide **144** to undergo cross coupling reaction (Scheme 39).

Mioskowski[80] reported a convenient synthesis of C(3)-substituted furans by reductive annulation of 1,1,1,-trichloroethyl propargyl ethers mediated by catalytic Cr(II) coupled to a Mn/TMSCl regeration system (Scheme 40).



Scheme 40

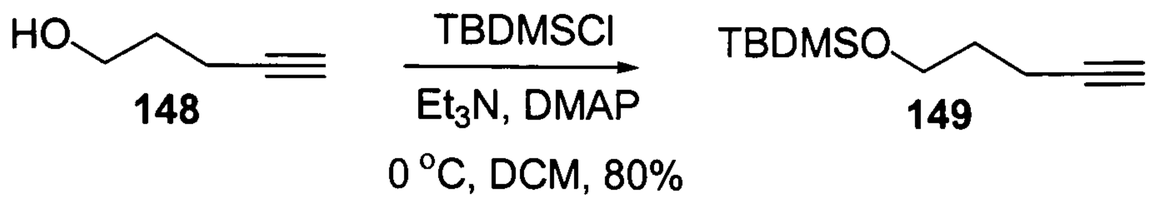
It was envisioned that desired alcohol **139** could be made possible by reductive annulation of trichloroether **152** using Mioskowski protocol following deprotection of the ensuing product **146** (Scheme 41). Ether **152** may be formed from a reaction between bromide **151** and trichloroethanol in the presence of a suitable base. Bromide **151** could be synthesized from bromination of alcohol **150**. Alkylation of alkyne **149** should furnish alcohol **150**. Protection of commercially available alcohol **148** should afford alkyne **149** (Scheme 41).



Scheme 41

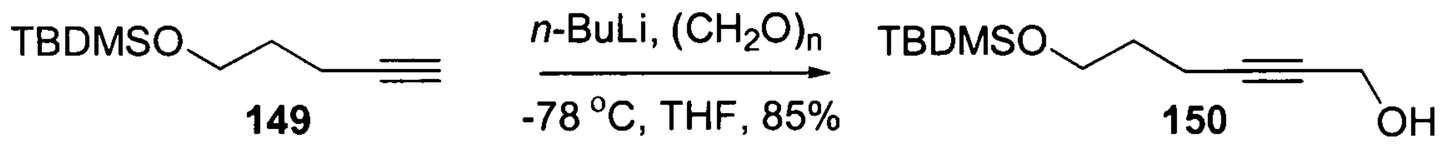
The reaction between alkyne **148** and *tert*-butyldimethylsilyl chloride in the presence of triethylamine and DMAP in DCM proceeded without incident. The crude reaction

was purified by flash column chromatography (4:1 hexane/diethyl ether) to afford compound **149** (9.4 g, 80%) as a colourless oil (Scheme 42).[81]



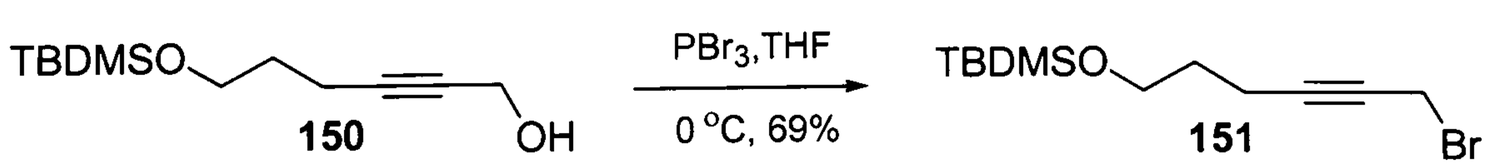
Scheme 42

Homologation of silylether **149** by one carbon using paraformaldehyde gave propargylic alcohol **150** in excellent yield (Scheme 43).[82] Alcohol **150** was used in the next step without further purification.



Scheme 43

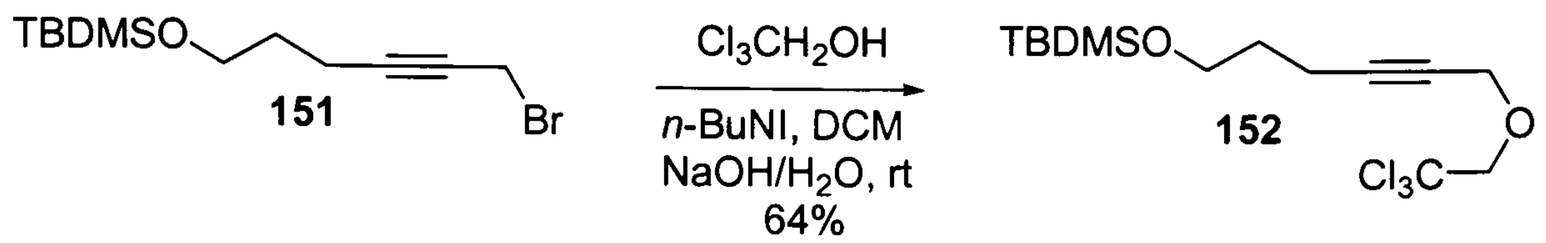
Direct bromination of alcohol **150** was best achieved using phosphorous tribromide in THF at 0 °C. The crude reaction was purified by column chromatography (10:1 hexane/diethyl ether) to afford bromide **151** (5.3 g, 69%) as a colourless oil (Scheme 44).[70]



Scheme 44

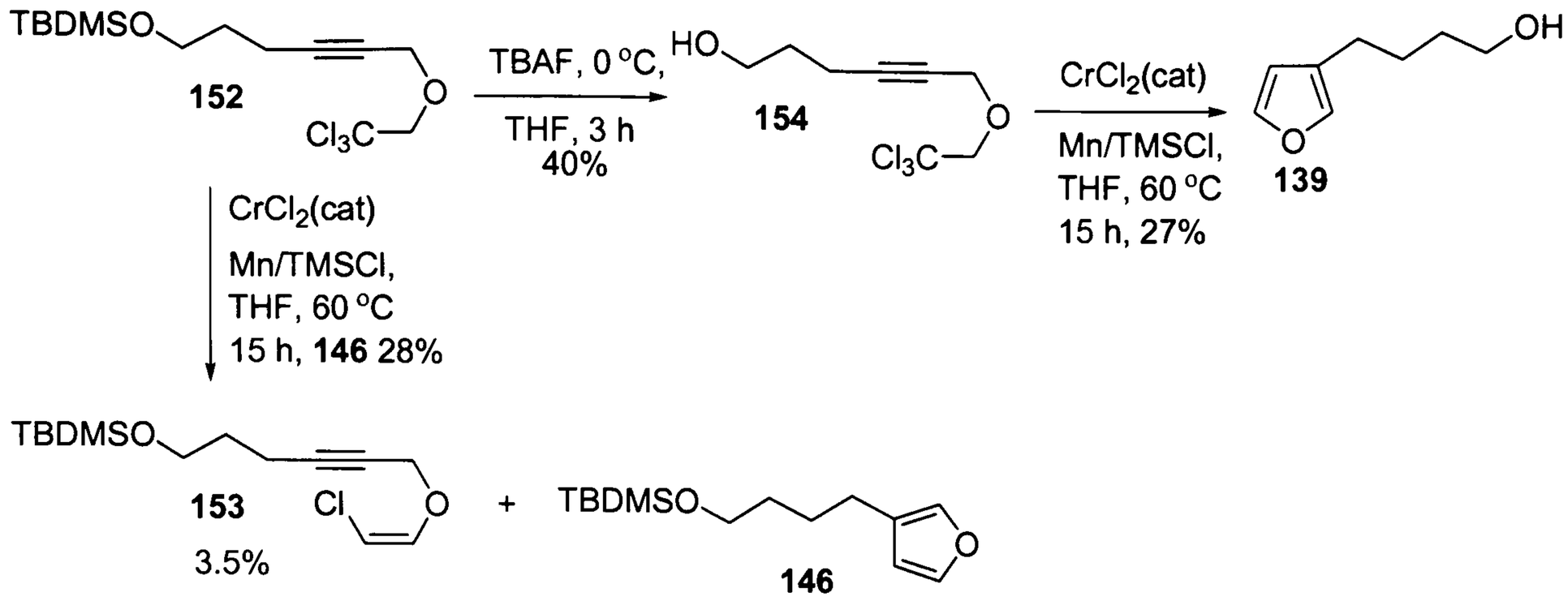
1,1,1-Trichloroalkyne **152** was prepared by alkylation of 2,2,2-trichloroethanol with propargyl bromide **151** at room temperature in the presence of NaOH/*n*-Bu_4NI in

dichloromethane (Scheme 45).[83] The reaction was purified by column chromatography (10% ethyl acetate in 60-80 petroleum ether) to furnish trichloroalkyne **152** (5.3 g, 64%) as a pale yellow oil.



Scheme 45

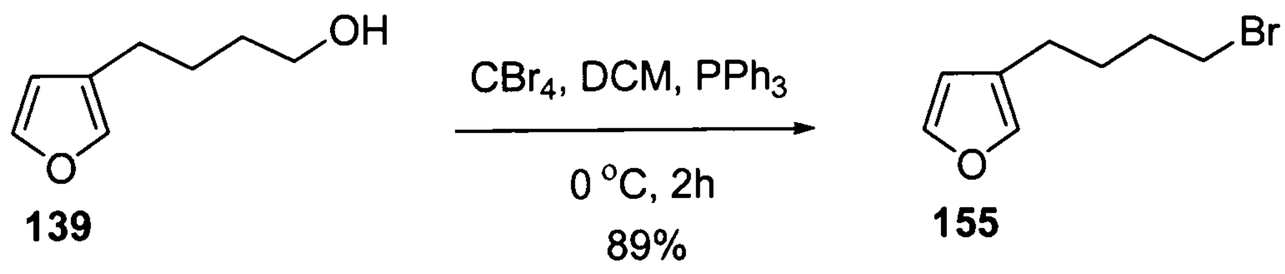
Attempted reductive annulation of protected ether **152** mediated by catalytic Cr(II) coupled to a Mn/TMSCl regeration system only gave 28% yield of desired furan **146** (Scheme 46).[83] In addition trace amounts of chloroenol ether **153** were isolated. In order to determine whether the presence of a protecting group has any influence on the yield of the reaction, compound **152** was deprotected. In the event, deprotection of **152** was effected by using tetrabutylammonium fluoride in tetrahydrofuran at 0 °C to give alcohol **154** in 40% yield (Scheme 46). Reductive annulation of alcohol **154** under the same conditions as compound **152** yielded only 27% of desired alcohol **139**. No starting material was recovered in the reaction (Scheme 46).[84]



Scheme 46

Given the unexpected results of Schemes **39** and **46**, hydroboration of alkene **138** (Scheme 32) was the preferred synthetic route to alcohol **139**.

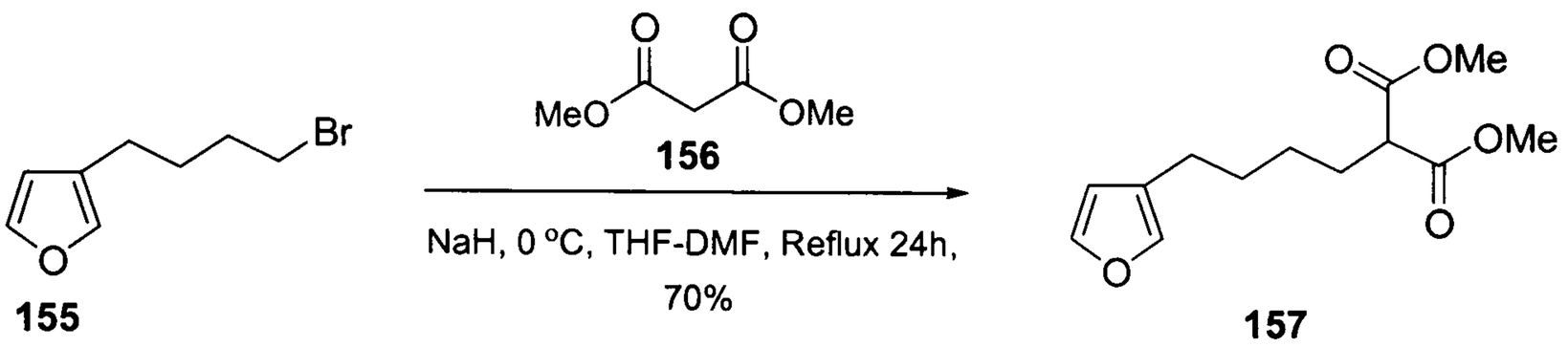
The synthesis of bromide **155** was not known in the literature, however using the methodology reported by Wang for direct bromination of alcohols, alcohol **139** was converted to bromide **155** using carbon tetrabromide in the presence of triphenylphosphine in excellent yield (Scheme 47).[68] The crude product was purified by column chromatography (8:1 60-80 petroleum ether/diethyl ether) to yield **155** as a colourless liquid.



Scheme 47

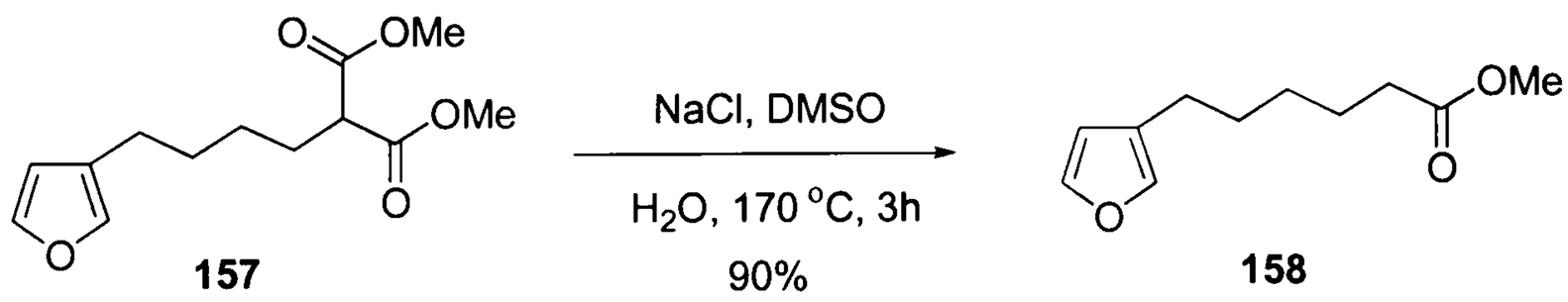
Although compound **157** was not known in the literature, it was readily prepared by alkylation of the *in-situ* generated anion of dimethylmalonate **156** with bromide **155**

under reflux for 24h (Scheme 48). The crude product could not be purified by column chromatography owing to the close proximity of the R_f values of the product and dimethylmalonate. Instead, the crude reaction mixture was subjected to a short-path distillation under reduced pressure to remove the excess dimethylmalonate, leaving essentially pure **157** (Scheme 48).[85]



Scheme 48

The decarboxylation of diester **157** to monoester **158** was readily achieved using the Krapcho protocol (Scheme 49).[86] The crude reaction mixture, obtained as a dense-yellow liquid, was purified by flash column chromatography (3:1 hexane/diethyl ether) to afford desired ester **158** as a colourless liquid in 90% yield (Scheme 49).

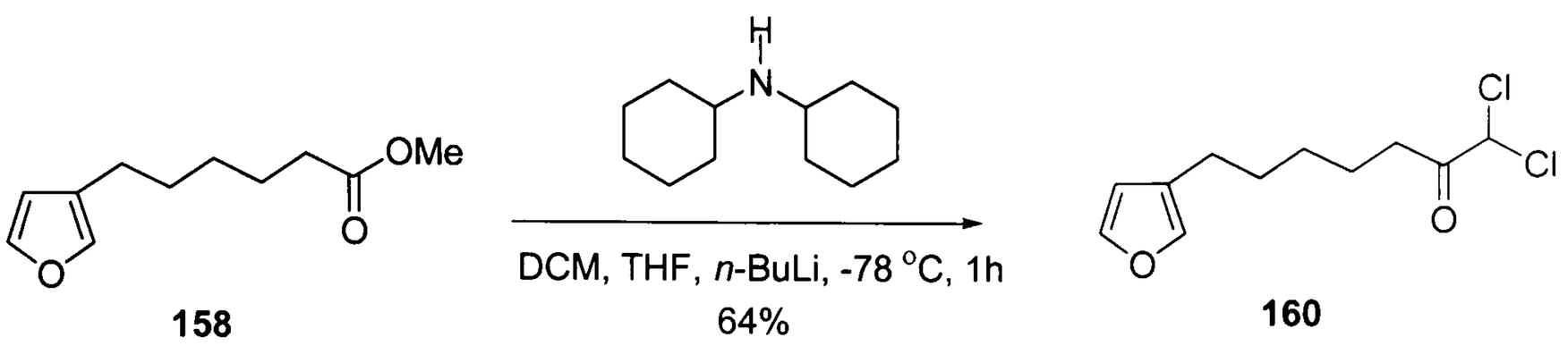


Scheme 49

2.2.1 Synthesis of dihaloketones 160/161

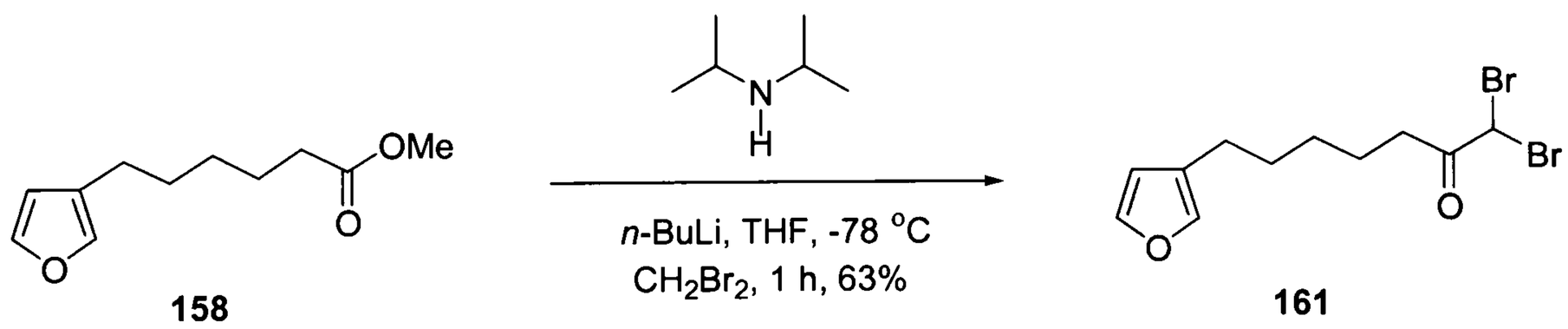
The synthesis of compound **160** was not known in the literature; however, using the methodology reported by Barluenga and co-workers for the preparation of dihalogeno ketones, direct deprotonation of dichloromethane using a solution of

dicyclohexylamide in THF at -78 °C, followed by quenching with **158** gave the requisite target compound **160** in good yield (Scheme 50).[87] Dichloroketone **160** was stable enough to be purified by column chromatography (10% ether in 60-80 petroleum ether).



Scheme 50

Dibromide **161** was prepared from ester **158** again using Barluenga's protocol (Scheme 51).[87] The crude reaction mixture was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to furnish dibromoketone **161** as a pale yellow oil in good yield. Dibromoketone **161**, unlike dichloroketone **160** was less stable in the neat form and had to be used instantly.



Scheme 51

2.2.2 Attempted Type-II [4+3] cycloaddition reaction of 160/161

Intramolecular Type-II [4+3] cycloaddition reaction of dibromide **161** and dichloride **160** were attempted under a variety of standard conditions, including $LiClO_4/Et_2O$, Et_3N/trifluoroethanol (TFE) and NaTFE/TFE (Table 1).[88]

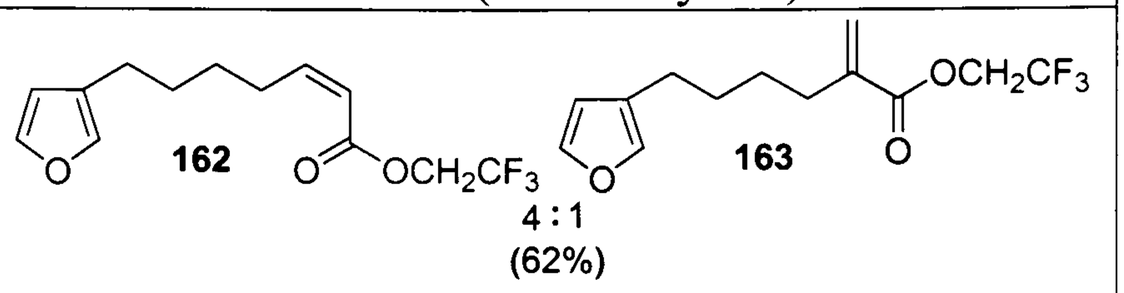
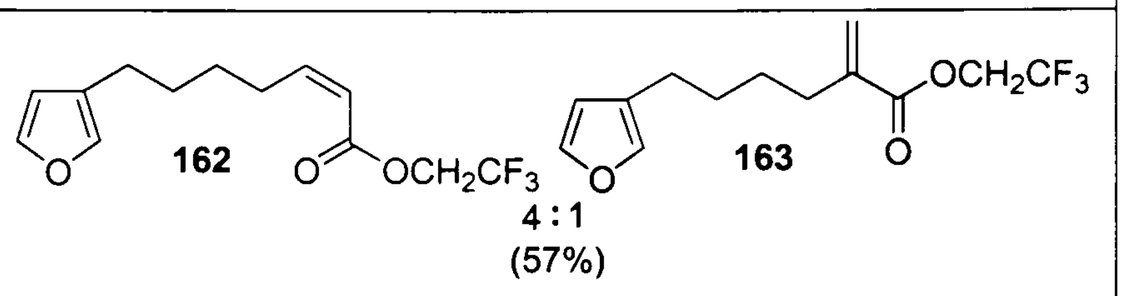
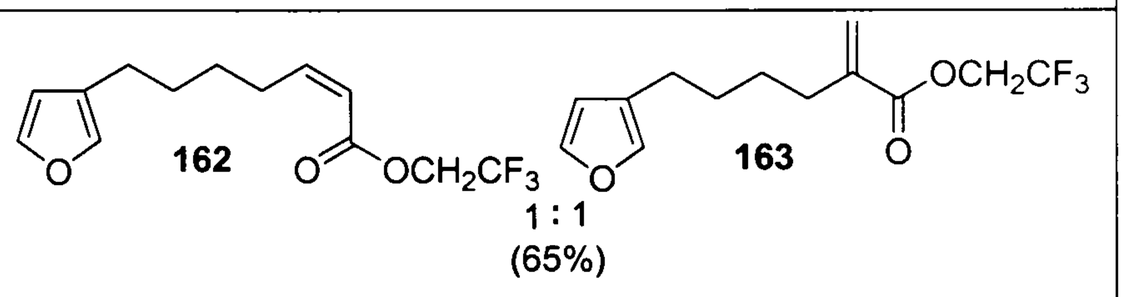
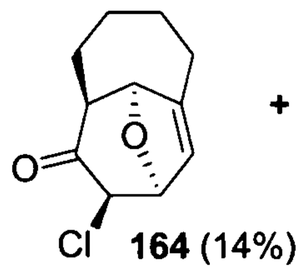
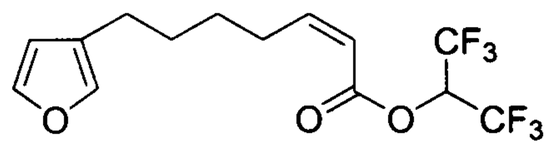
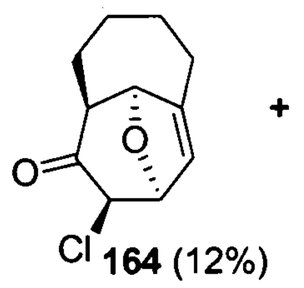
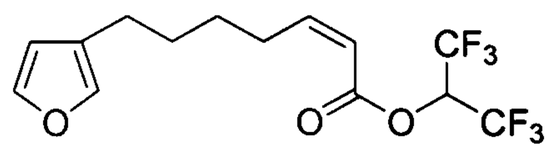
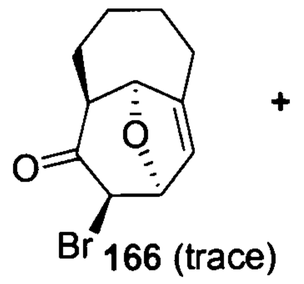
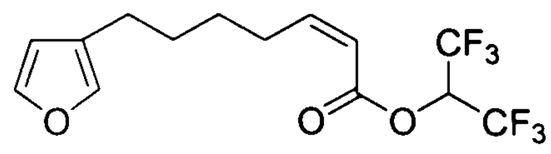
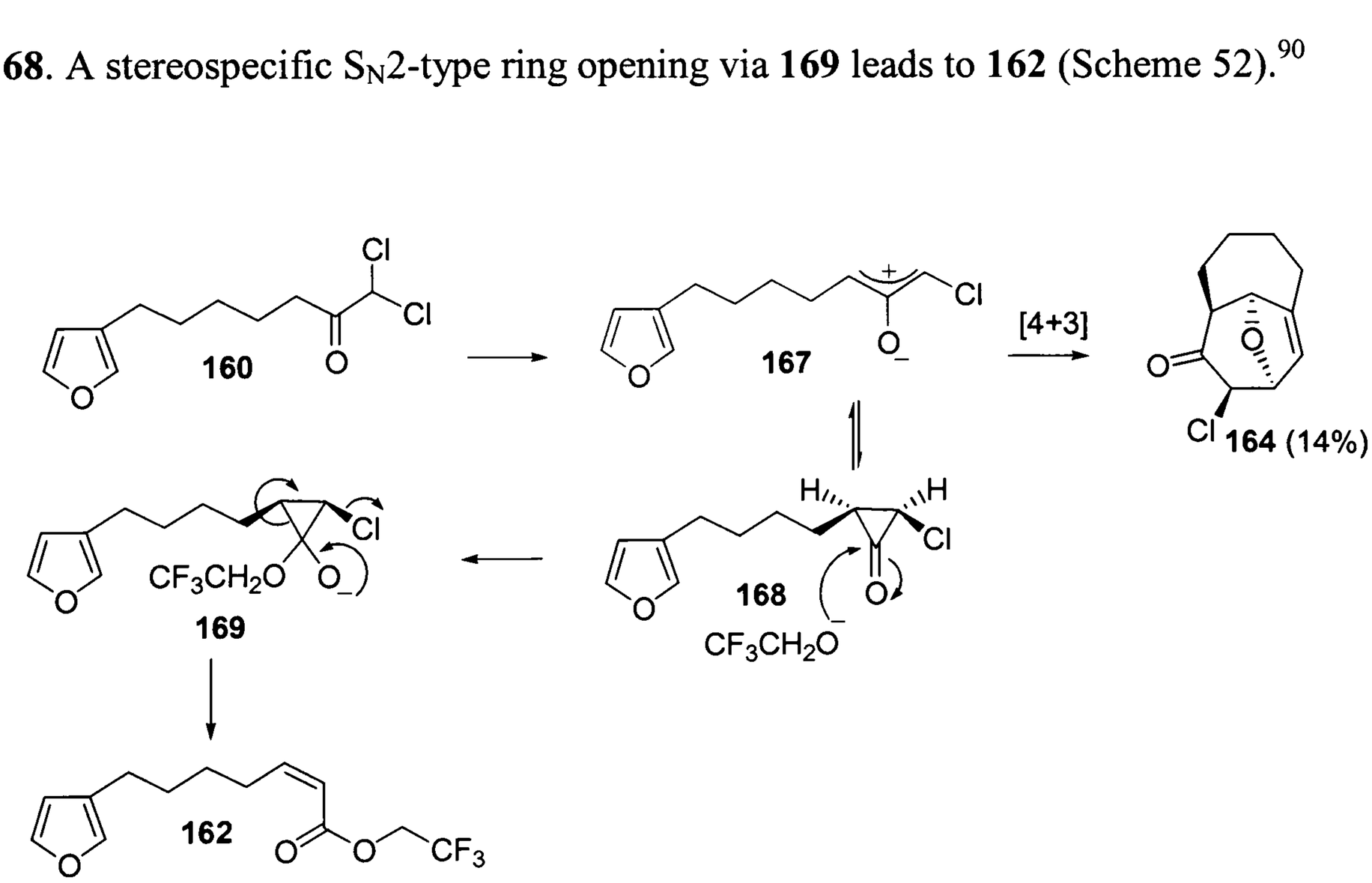
Entry	Ketone	Conditions	Product (isolated yield)
1	**160** X = Cl	Et_3N(2.2eq), TFE(0.17M) rt, 1 week	 4 : 1 (62%)
2	**160** X = Cl	Et_3N(2.2eq), TFE(0.8M) 50 °C, 24 h	 4 : 1 (57%)
3	**160** X = Cl	NaTFE/ TFE(0.8M) rt, 5 days	 1 : 1 (65%)
4	**160** X = Cl	Et_3N(2.2eq) $(CF_3)_2CHOH$ (0.8M) r.t, 1 week	 **164** (14%) +  **165** (trace)
5	**160** X = Cl	$NaOCH(CF_3)_2$ / $(CF_3)_2CHOH$ (0.8M) r.t, 5 days	 **164** (12%) +  **165** (3%)
6	**161** X = Br	Et_3N(2.2eq) $(CF_3)_2CHOH$ (0 .8M) r.t, 1 week	 **166** (trace) +  **165** (65%)

Table 1

In general reactions proceeded slowly at room temperature to give complex mixtures of products. Analysis of ^{1}H NMR of the crude reaction mixtures suggested retention of the monosubstituted furan functionality under almost all conditions.[89] Reactions in trifluoroethanol slowly converted to a mixture of trifluoroethyl acrylic esters **162** and **163**, the ratio of which varied with the base used to generate the oxyallyl cation (Table 1, entries 1-3). For example, by changing the base from triethylamine (entries 1 and 2) to NaTFE (entry 3) the ratio of acrylic esters **162** and **163** changed from 4:1 to 1:1.

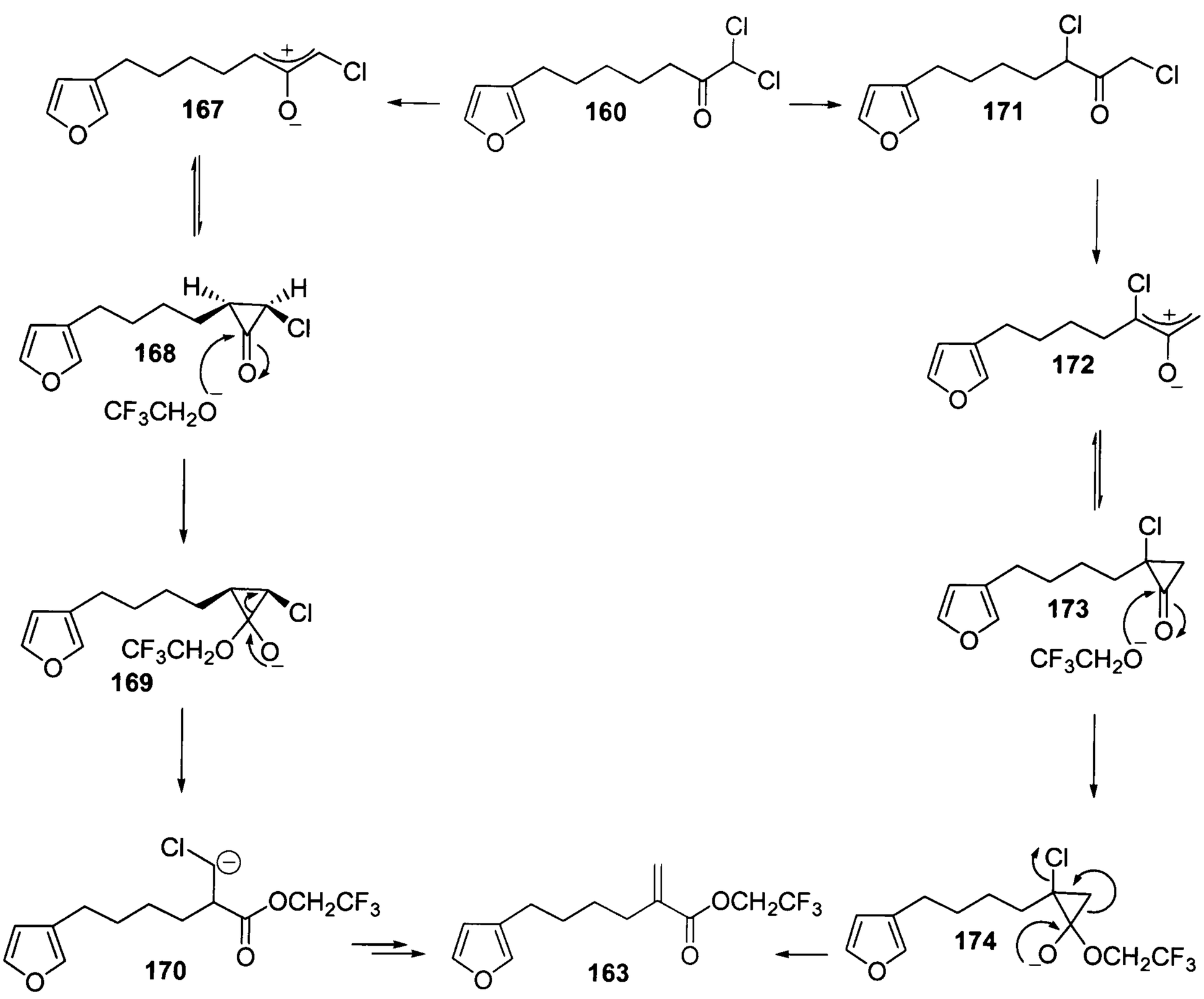
The formation of **162** and **163** was ascribed to a competing Favorskii rearrangement in preference to the desired [4+3] cycloaddition reaction (Schemes 52 and 53). The *cis*-double bond geometry in **162** was assigned on the basis of coupling constants in the ^{1}H NMR spectrum and is consistent with thermally allowed electrocyclic ring closure of the oxyallyl cation **167** in its preferred W configuration to give *cis* cyclopropane **168**. A stereospecific S_N2-type ring opening via **169** leads to **162** (Scheme 52).[90]



Scheme 52

The formation of ester **163** can be attributed to elimination of an α-chloromethyl ester **170** (upon proton migration) formed via opening of the alternative C-C bond in the

cyclopropane intermediate **169** or via Favorskii rearrangement of a 1,3-dichloroketone formed via 1,3-Cl migration in **160** (**171** to **174** Scheme 53).



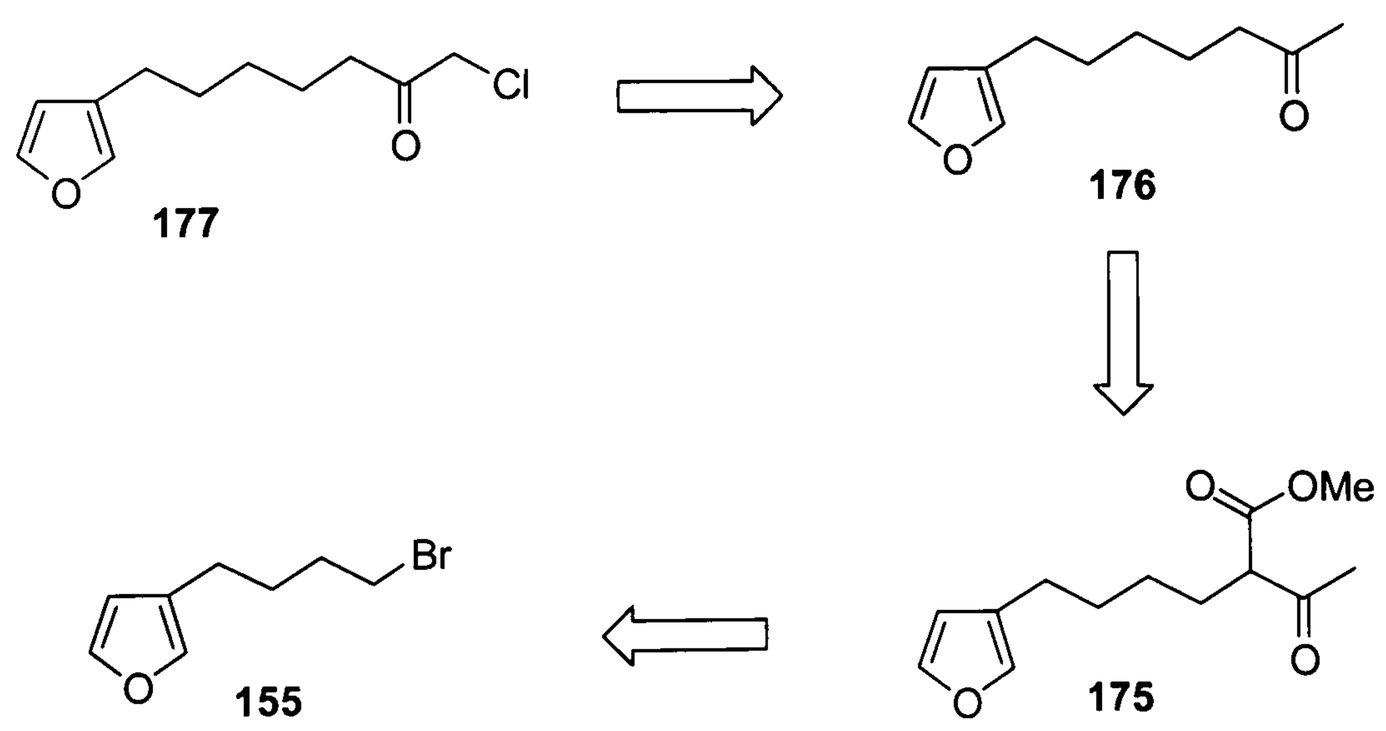
Scheme 53

Products derived from Favorskii rearrangement have been observed as minor components in [4+3] cycloaddition reactions of oxyallyl cations,[91] but their formation is minimised by the use of the non nucleophilic solvent, trifluoroethanol. Recourse to the even less nucleophilic solvent hexafluoropropan-2-ol suppressed the Favorskii rearrangement of dichloroketone **160** and promoted formation of the desired cycloadduct **164** (albeit in low yield), thus establishing for the first time that the Type-II [4+3] cyclisation mode is possible (Table 1, entries 4 and 5). Application of these

conditions to dibromoketone **161** only gave trace amounts of the desired cycloadduct **166**, with *cis*-alkene **165** now predominating (Table 1, entry 6).

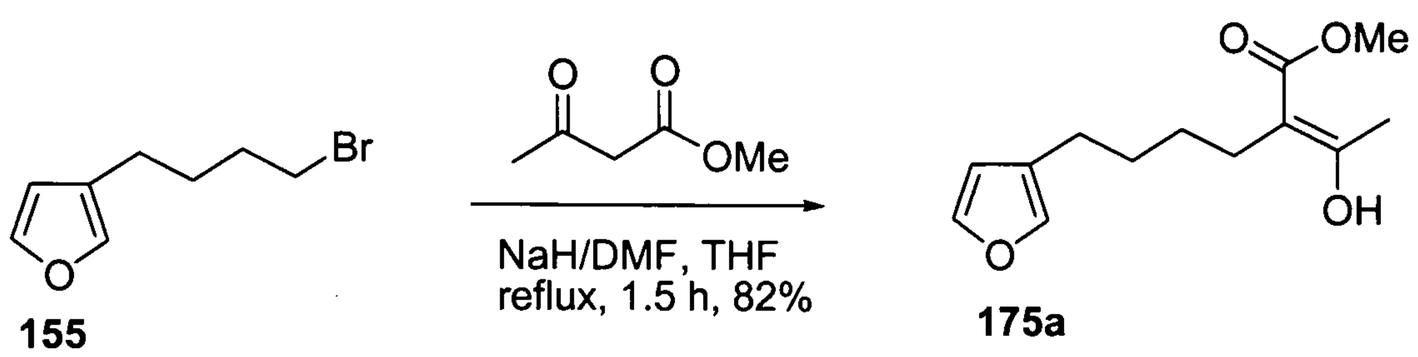
Given the unexpected results with dichloroketone **160** and dibromoketone **161** (Table 1), it was hoped that monochloroketone **177** bearing one chlorine atom would eliminate the Farvoskii rearrangement and increase the possibility of [4+3] cyclisation. Furthermore, cyclisation of **177** would lead directly to cycloadduct **134** (Scheme 25) thereby reducing the number of steps by one transformation in comparison to successful cyclisation of dihaloketones **160** and **161**. A retrosynthetic analysis of monochloroketone **177** is depicted in Scheme 54.

It was hoped that α-monochloroketone **177** could be synthesised from chlorination of ketone **176**. Decarboxylation of ketoester **175** should deliver ketone **176**. Ester **175** may be prepared from a reaction between bromide **155** and methyl acetoacetate (Scheme 54).



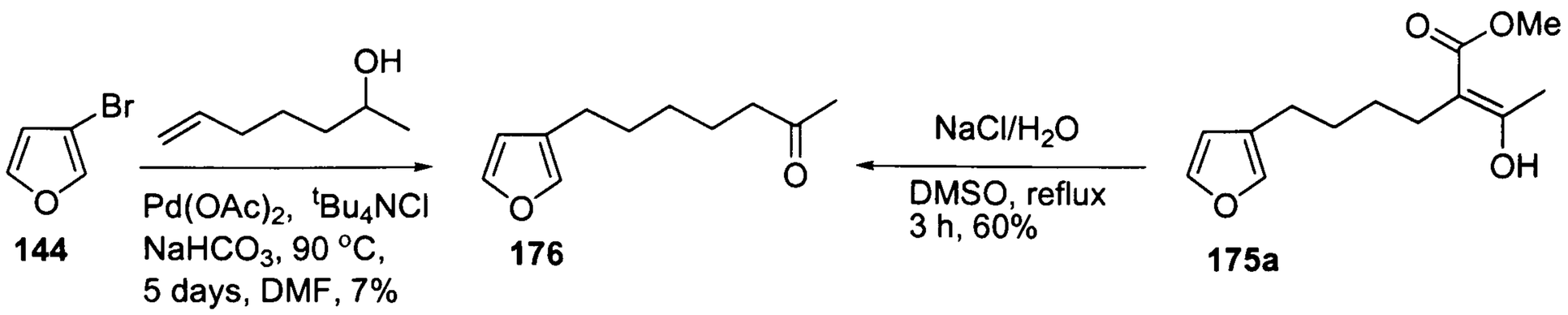
Scheme 54

Although ketoester **175** was not a known compound, it was readily prepared as the enol **175a** by alkylation of the *in-situ* generated dianion of methyl acetoacetate with **155** under reflux for 1.5 h. The crude reaction mixture was purified by a short-path distillation under reduced pressure (2 mm/Hg, 80-95 °C) to remove the excess methyl acetoacetate, leaving essentially pure enol **175a** as a pale yellow oil (Scheme 55).[85]



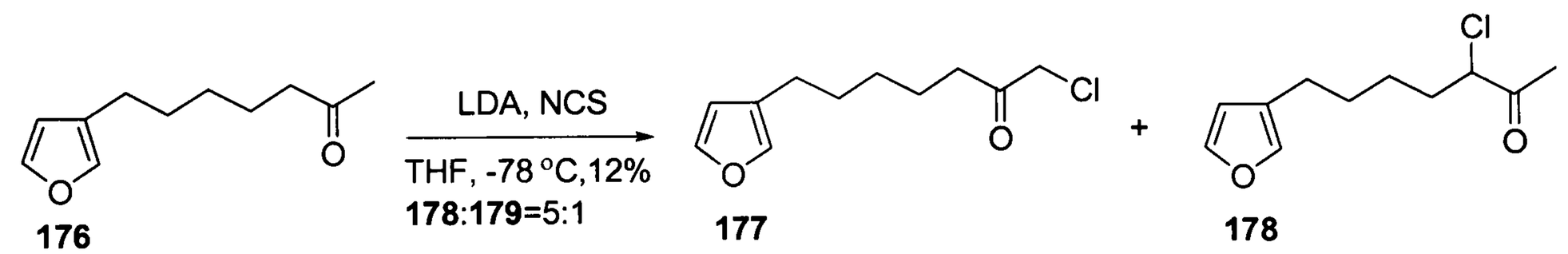
Scheme 55

The decarboxylation of enol **175a** to ketone **176** was readily achieved using the Krapcho protocol (Scheme 56).[86] The crude reaction was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to afford 60% yield of the desired product **176** as a pale yellow oil. An attempted formation of **176** via a cross coupling/alkene migration reaction between bromide **144** and 1-hepten-6-ol proved problematic. The reaction was messy (by TLC) and purification of the crude reaction by column chromatography (4:1 hexane/diethyl ether) only gave 7% of desired ketone **176** and 50% of the starting alcohol. Hence, decarboxylation of compound **175a** was the preferred synthetic route to **176** (Scheme 56).



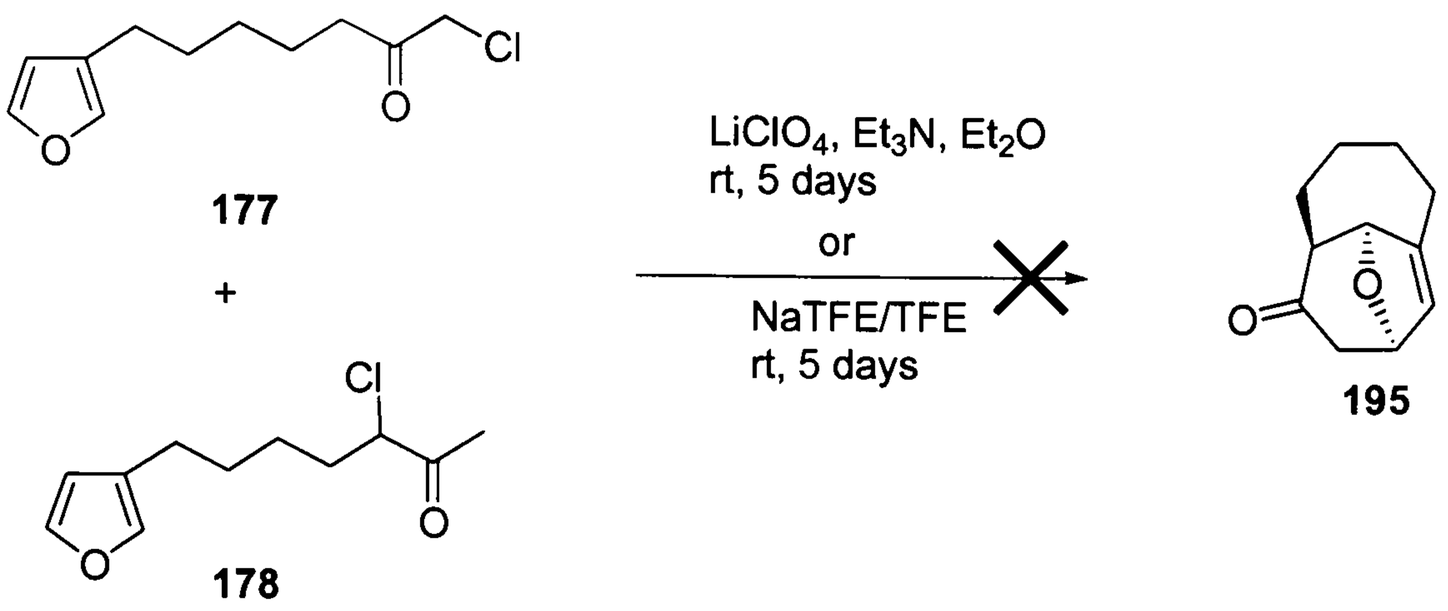
Scheme 56

Direct chlorination of ketone **176** gave an inseparable mixture of desired chloroketone **177** and ketone **178** in 12% overall yield in a 5:1 ratio (Scheme 57).[92] Better yields were obtained when ester **158** was chloromethylated using lithium diisopropylamide and chloroiodomethane in the presence of acetic acid to afford an inseparable mixture of **177** and **178** in 27% yield in a 5:1 ratio (by ^{1}H NMR analysis).[93] Compound **178** could also undergo the [4+3] cyclisation to give desired cycloadduct **195,** therefore its formation was not deemed detrimental (Scheme 57).



Scheme 57

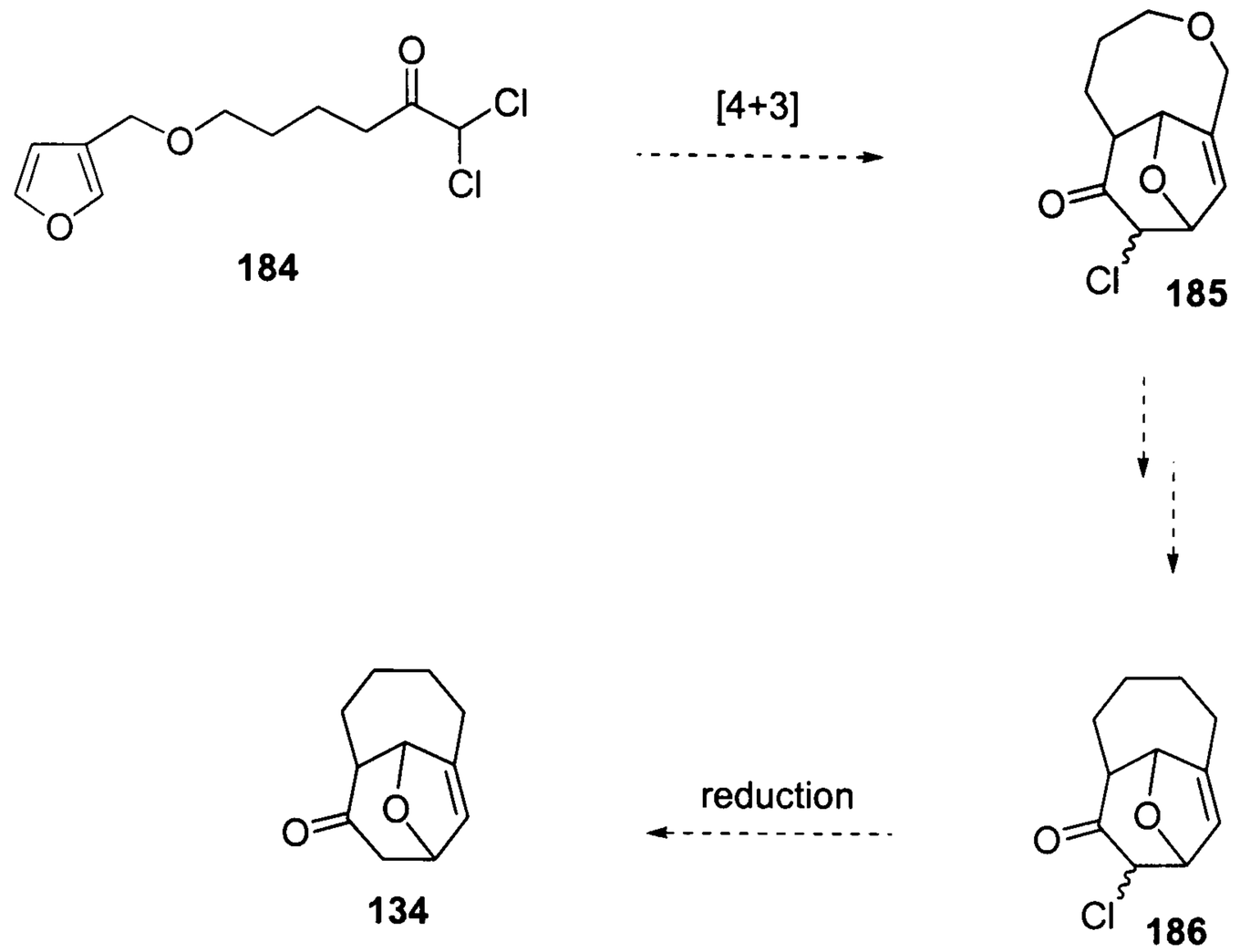
Attempted [4+3] cyclisation of chloroketones **177** and **178** under $LiClO_4/Et_3N/Et_2O$ or NaTFE/TFE conditions gave recovered starting material and none of desired adduct **195** (Scheme 58).



Scheme 58

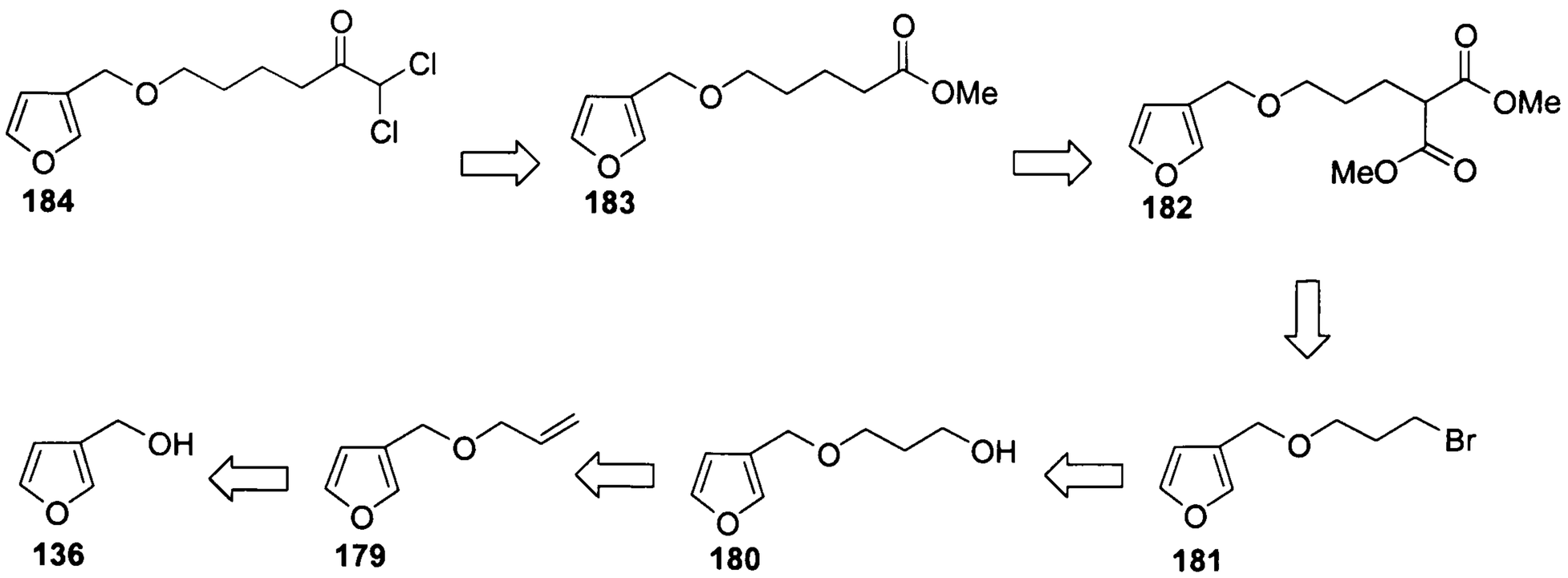
One possible reason for the lack of cyclisation of dihaloketones **160/161** and monochloroketones **177/178** could be as a result of the strain generated in bringing together the furan ring and the allylic cation. In order to test this hypothesis, the chain separating the furan ring and the allylic cation was extended by one atom. It was hoped that insertion of an oxygen atom into the chain would be suitable for this purpose. Towards that end, synthetic studies leading to the preparation of compound **184** were undertaken.

It was anticipated that cycloadduct **185** could be made possible from a [4+3] cycloaddition reaction of **184**. Compound **185** could then be converted into **186** through a sequence of reactions involving ring contraction. Reduction of **186** should deliver desired cycloadduct **134** (Scheme 59). Additionally, the synthesis of **184** should be possible using much of the methodology used for the synthesis of dihaloketones **160** and **161**.



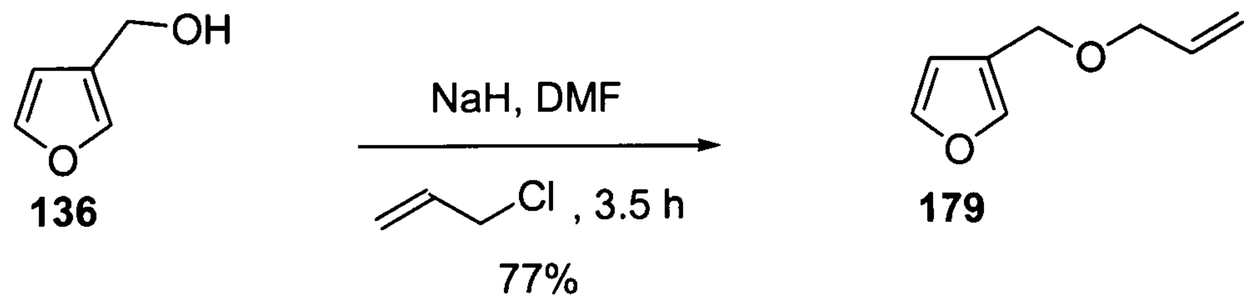
Scheme 59

A retrosynthetic analysis of **184** is outlined in Scheme 60. Dichloroketone **184** may be prepared from a reaction between ester **183** and dichloromethane. Ester **183** could be made possible from decarboxylation of diester **182**. A reaction between bromide **181** and dimethyl malonate should deliver diester **182**. Bromination of alcohol **180** should render bromide **181**. Hydroboration of alkene **179** followed by oxidative work-up should bring in hand alcohol **180**. Etherification of alcohol **136** using allyl chloride should furnish alkene **179** (Scheme 60).



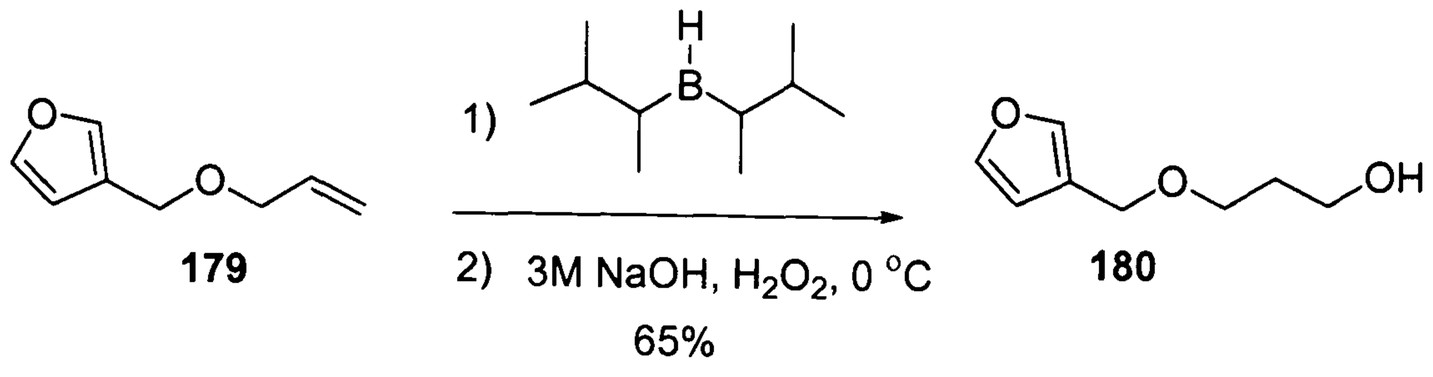
Scheme 60

The synthesis of **179** is not known in the literature. However, using the methodology reported by Greeves[94] ether **179** could be readily prepared from alcohol **136** using NaH in *N,N*-dimethylformamide in the presence of allylchloride at room temperature for 3.5 hours. Under these conditions ether **179** was obtained in 77% yield (Scheme 61). The crude product was purified by distillation using a Kugelrohr apparatus (bp.50-70 °C, 2mm/Hg).



Scheme 61

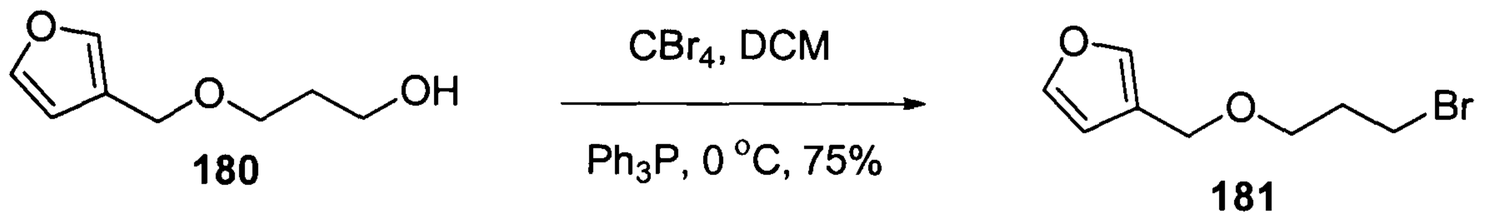
Selective hydroboration of **179** was effected by treatment with a freshly prepared solution of disiamylborane followed by hydrolysis using 3M sodium hydroxide and 27% hydrogen peroxide to give **180** in 65% yield. The crude product was purified by column chromatography (3:2 60-80 petroleum ether/diethyl ether) to afford alcohol **180** as a colourless oil (Scheme 62).[69]



179 **180**

Scheme 62

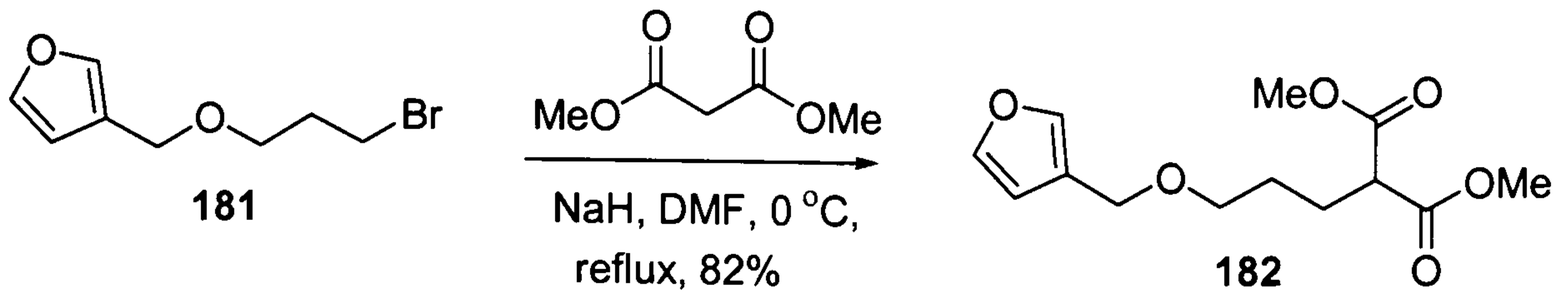
Bromide **181** is not a known compound in the literature. However it could readily be prepared by direct bromination of alcohol **180** using carbon tetrabromide in dichloromethane in the presence of triphenylphosphine at 0 °C for 2h. The crude reaction mixture was purified by column chromatography using (4:1 60 80 petroleum ether/diethyl ether) to afford bromide **181** in 75% yield (Scheme 63).[68]



180 **181**

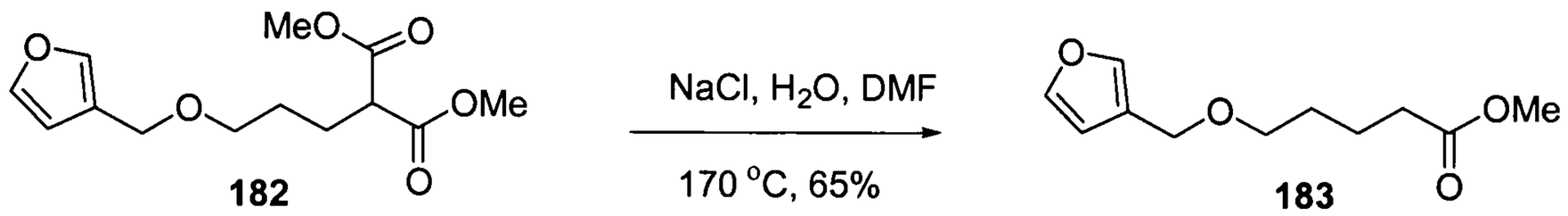
Scheme 63

The synthesis of **182** is not known in the literature however, alkylation of dimethylmalonate using bromide **181** in the presence of NaH delivered the required diester **182** in excellent yield (Scheme 64).[68] Purification of the crude reaction mixture proved problematic owing to the close proximity in R_f values of diethylmalonate and the product. Although a short-path distillation of the crude reaction mixture removed most of the excess dimethylmalonate, ^{1}H NMR analysis after distillation showed **182** still contaminated with some dimethylmalonate. However, all of the dimethylmalonate contaminants were destroyed in the next step (Scheme 64).



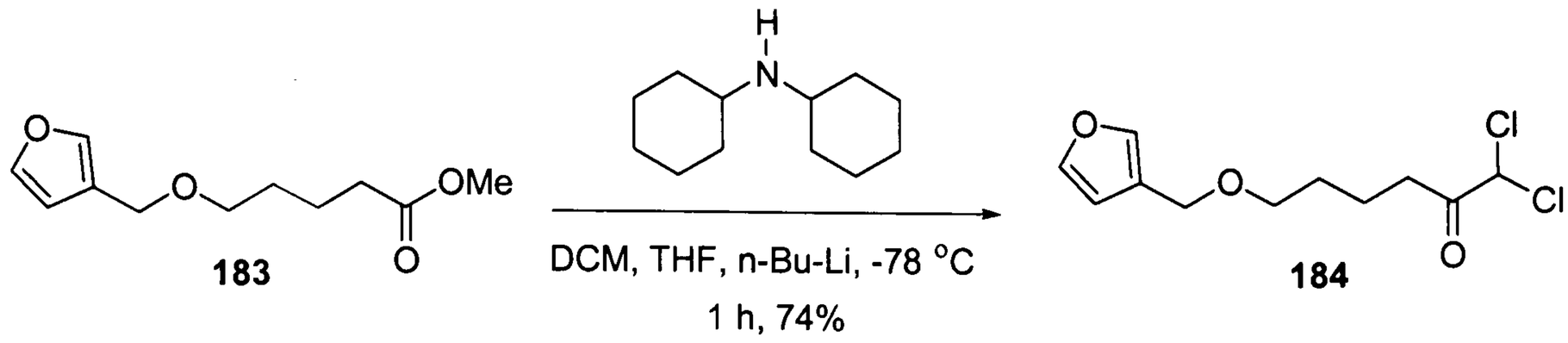
Scheme 64

Decarboxylation of diester **182** to ester **183** using sodium chloride in wet *N*,*N*-dimethylformamide at elevated temperatures was straightforward. The crude reaction mixture was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to afford the required ester **183** in good yield (Scheme 65).[86]



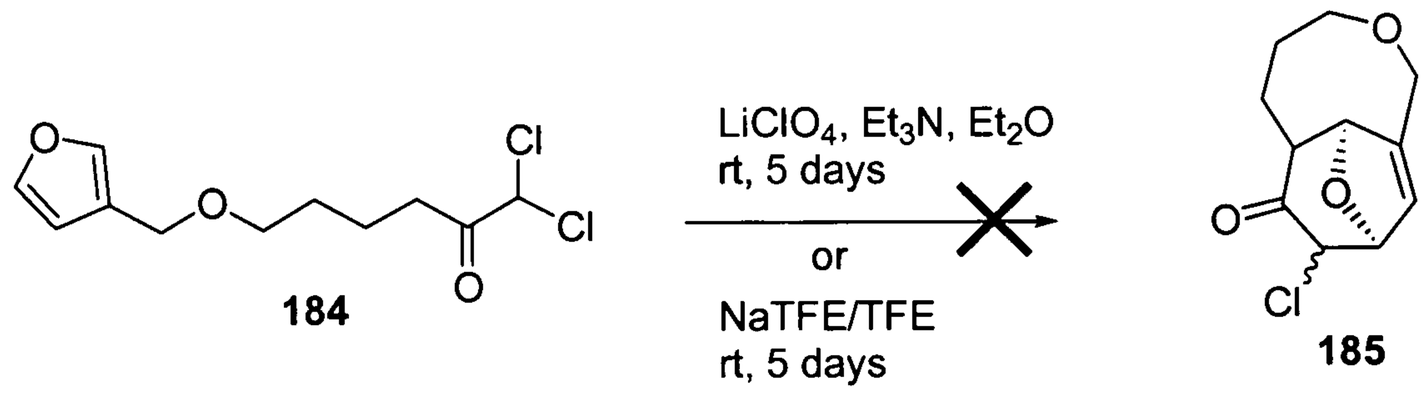
Scheme 65

The synthesis of dichloroketone **184** was not known in the literature. However, it was readily prepared by deprotonation of dichloromethane using *in-situ* generated lithium dicyclohexylamide in THF at –78 °C and then quenching with ester **183** to give the dichloroketone **184** in excellent yield (Scheme 66).[87] Dichloroketone **184** was stable enough for it to be purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether).



Scheme 66

Attempted intramolecular [4+3] cyclisation of dichloroketone **184** to adduct **185** could not be accomplished under $LiClO_4$/ Et_3N/Et_2O or NaTFE/TFE conditions (Scheme 67). TLC analysis of the crude reaction showed mainly polymeric residue on the base line. ^1H NMR of the crude reaction showed trace amounts of unsaturated acrylic esters presumably resulting from the Favoskii rearrangement.



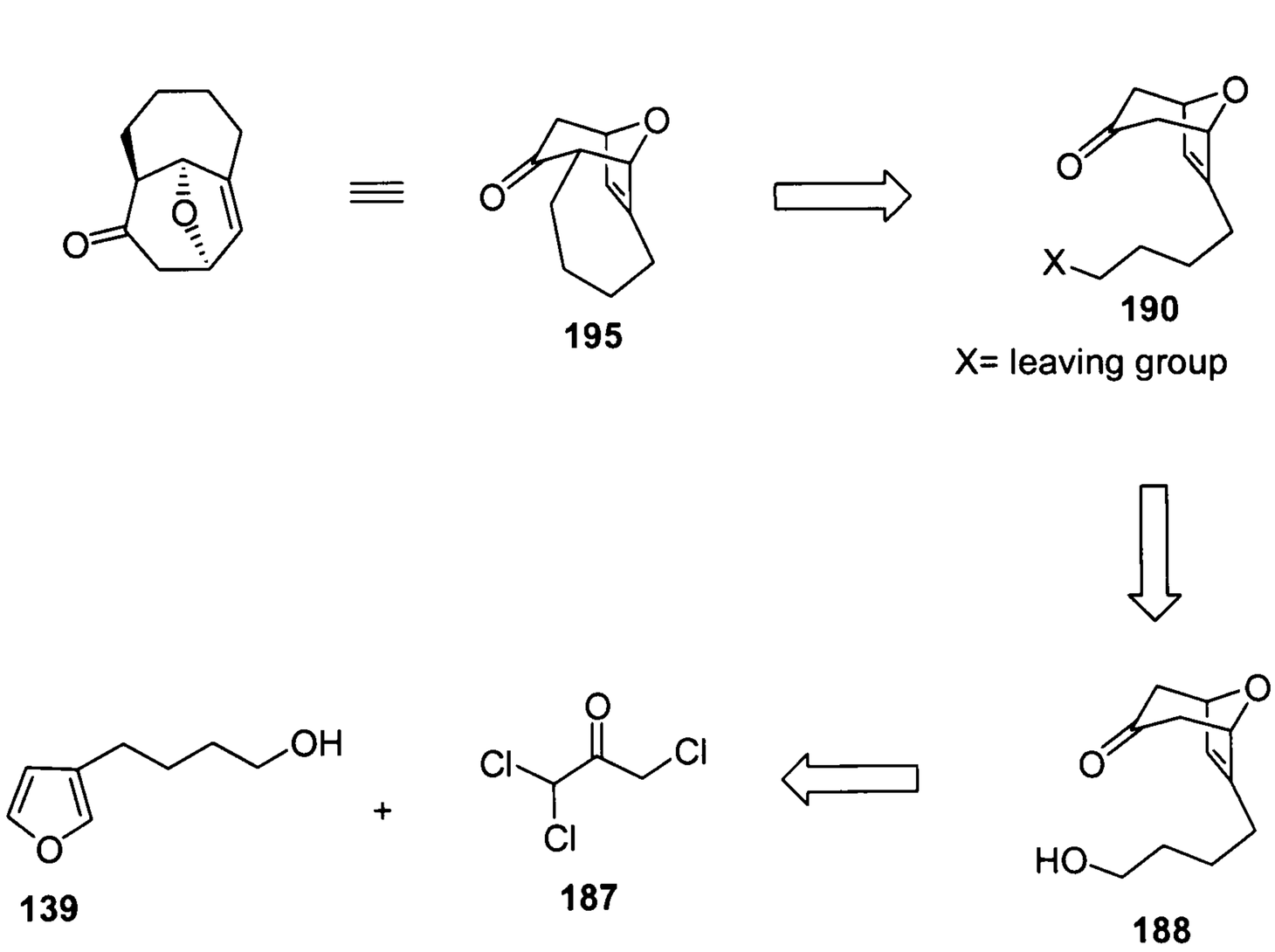
Scheme 67

The results in Table 1 clearly indicate that the Type-II [4+3] cyclisation mode is possible although it is never going to be synthetically viable under these reaction conditions. Furthermore, the unexpected results shown in Schemes 58 and 67 called for a change in the synthetic strategy to **195**, although there are a variety of alternative substrates for oxyallyl cation generation that might avoid the problem of competing Favorskii rearrangement.[95] Instead, a complementary approach involving an

intramolecular enolate alkylation to close a seven membered ring system was investigated (Scheme 68).[96]

2.2.3 Synthetic alternative to the Type-II [4+3]cyclisation

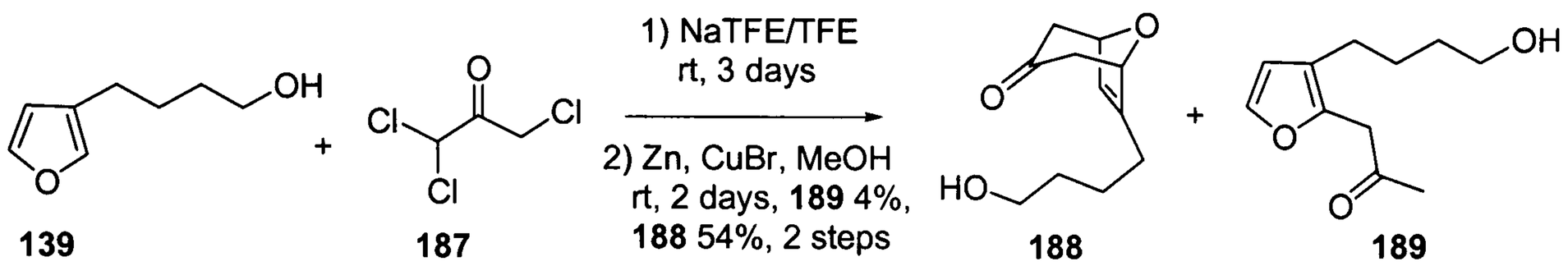
It was anticipated that required tricyclic ketone **195** could be synthesised via intramolecular alkylation of ketone **190**. Analysis of simple molecular models suggested that the conformation required for the S_N2 reaction to occur is only accessible on the face of the enolate opposite the oxygen bridge of **190**. A reaction between alcohol **188** and a suitable electrophile should render compound **190**. An intermolecular [4+3] cycloaddition reaction between alcohol **139** and 1,1,3-trichloropropan-2-one **187** should provide alcohol **188** after dehalogenation (Scheme 68).



Scheme 68

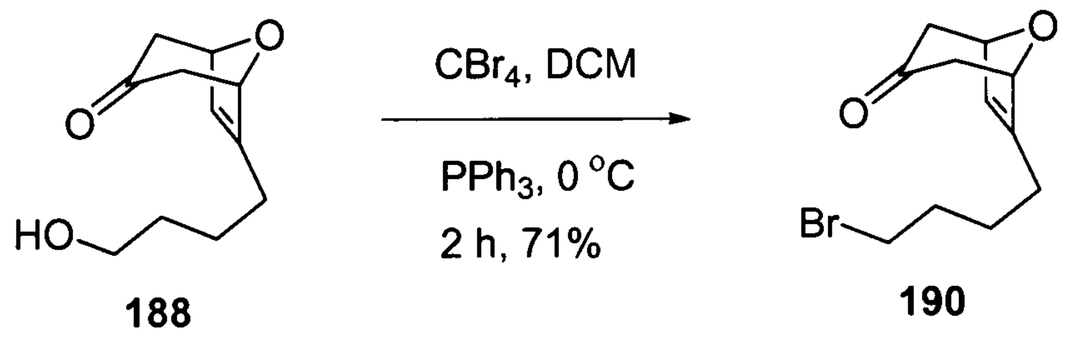
The intermolecular [4+3] cyclisation reaction between furan **139** and trichloropropan-2-one **187** in the presence of NaTFE/TFE proceeded at room temperature to give a

residue that was taken up in methanol and dehalogenated using Zn-Cu couple. The crude reaction was purified by column chromatography (3:1 60-80 petroleum ether/ethyl acetate) to afford 4% of disubstituted furan **189** accompanied by 54% of desired alcohol **188** (Scheme 69).[88] Formation of disubstituted furan **189** is attributed to a stepwise mechanism between furan **139** and the *in situ* generated oxyallyl cation from **187** (Scheme 69).



Scheme 69

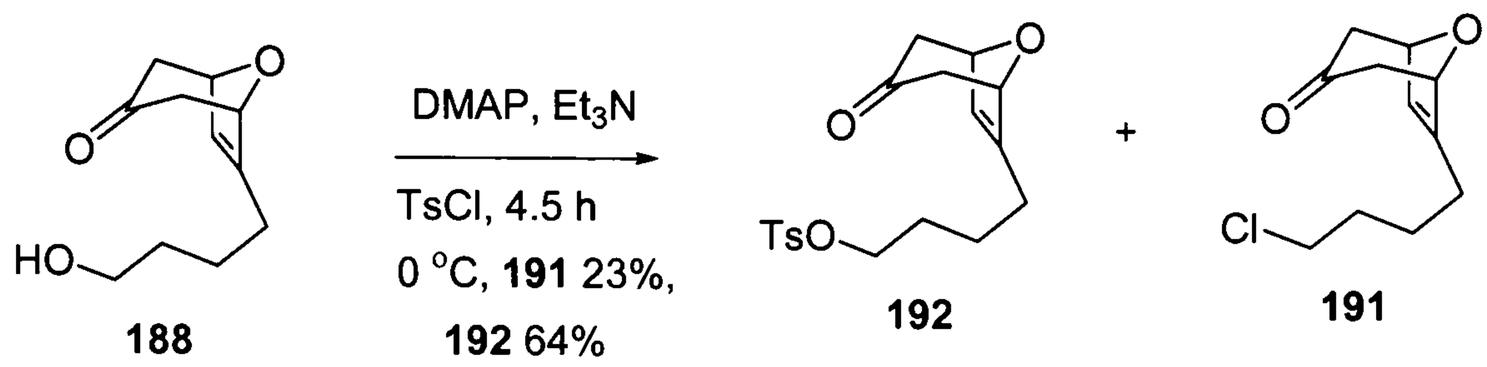
Direct bromination of alcohol **188** was accomplished using carbon tetrabromide in dichloromethane in the presence of triphenylphosphine at 0 °C (Scheme 70). The excess triphenyphosphine oxide was removed by column chromatography (2:1 60-80 petroleum ether/ethyl acetate) to provide bromide **190** in 71% yield (Scheme 70).[68]



Scheme 70

Tosylation of alcohol **188** was effected using triethylamine in the presence of DMAP and tosyl chloride in dichloromethane at 0 °C. The use of excess tosyl chloride (1.7 eq) prompted a side reaction which resulted in the formation of 23% of chloride **191**

along with 64% of required tosylate **192**. Since chloride **191** could potentially be converted into desired tricyclic ketone **195**, its formation in the reaction was not deemed detrimental (Scheme 71).

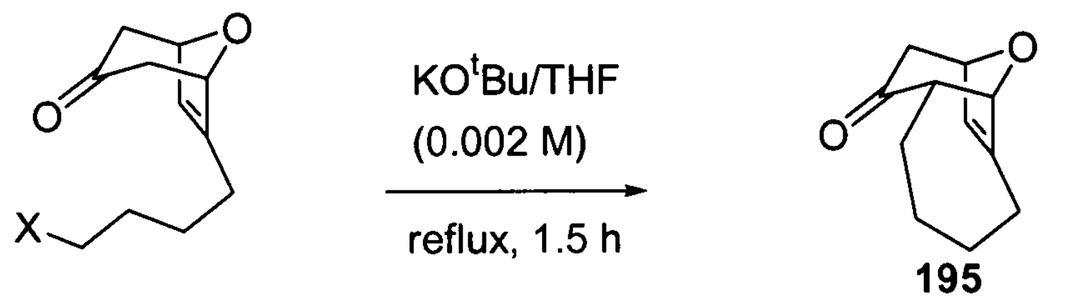


188 **192** **191**

Scheme 71

2.2.4 Synthesis of tricyclic ketone 195

Seven membered ring closure was attempted using a variety of bases (KH, NaH, LDA, KHMDS, Cs_2CO_3, KO-*t*-Bu) and conditions (solvent/temperature) on bromide **190**, chloride **191** and tosylate **192** (Table 2).[96]



195

Scheme 72

Attempted alkylation of bromide **190** using LDA, NaH or Cs_2CO_3 (entries 1, 3 and 6, Table 2) gave recovered starting material and none of the desired ketone **195**. In the case of KHMDS (entry 5) complete decomposition of the starting material was observed. The use of KH with bromide **190** at 0 °C gave an acceptable yield of **195**

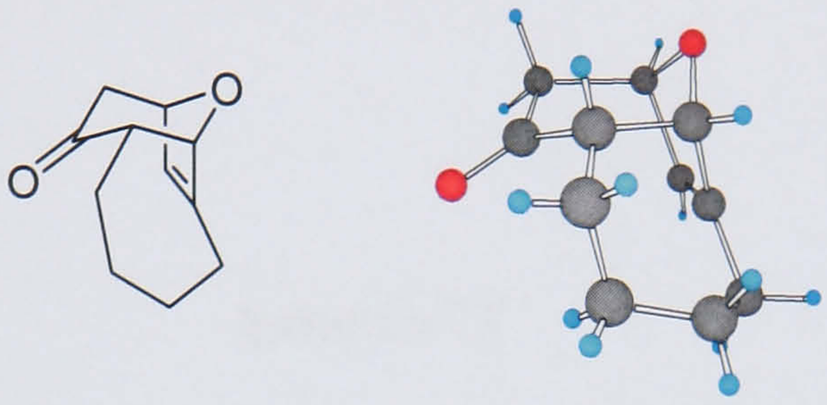
(entry 2). In general KO-*t*-Bu in refluxing tetrahydrofuran under high dilution conditions proved greatly superior to other bases. Under these conditions chloride **191**, bromide **190** and tosylate **192** were closed to ketone **195** in 42, 60 and 80% yield respectively (entries 8, 7 and 10). Prolonged reactions led to degradation of **195** (entry 9, Table 2).

Entry	substrate	Conditions	Yield of **195** (%)
1	Bromide **190**	LDA (1.3eq), -78 °C, THF (0.05 M), 2h	0
2	Bromide **190**	KH (2eq), THF (0.02 M), 0 °C, 25min	56
3	Bromide **190**	NaH (2eq), rt, THF (0.02 M), 24h	0
4	Tosylate **192**	NaH (1eq), DME (0.1 M), reflux, 18h.	0
5	Bromide **190**	KHMDS (2eq), THF (0.01 M), -40 °C, 2h	No reaction and no recovered starting material
6	Bromide **190**	Cs_2CO_3 (4.9eq), TBAI (2eq), CH_3CN, 60 °C, 2h	0
7	Bromide **190**	KO^tBu (2eq), THF (0.002 M), reflux, 1.5h	60
8	Chloride **191**	KO^tBu(2eq), THF(0.002 M), reflux, 1.5h	42
9	Tosylate **192**	KO^tBu (1.2eq), THF (0.002 M), reflux, 3h	60
10	Tosylate **192**	KO^tBu (2eq), THF (0.002 M), reflux, 1.5h	80

Table 2

2.2.5 X-ray structure of 195

The structure of **195** was unambiguously proven by X-ray crystallography (Figure 5). Compound **195** in the solid state adopts a chair conformation in the tetrahydropyran ring, placing the connecting chain in an equatorial position (Figure 5).

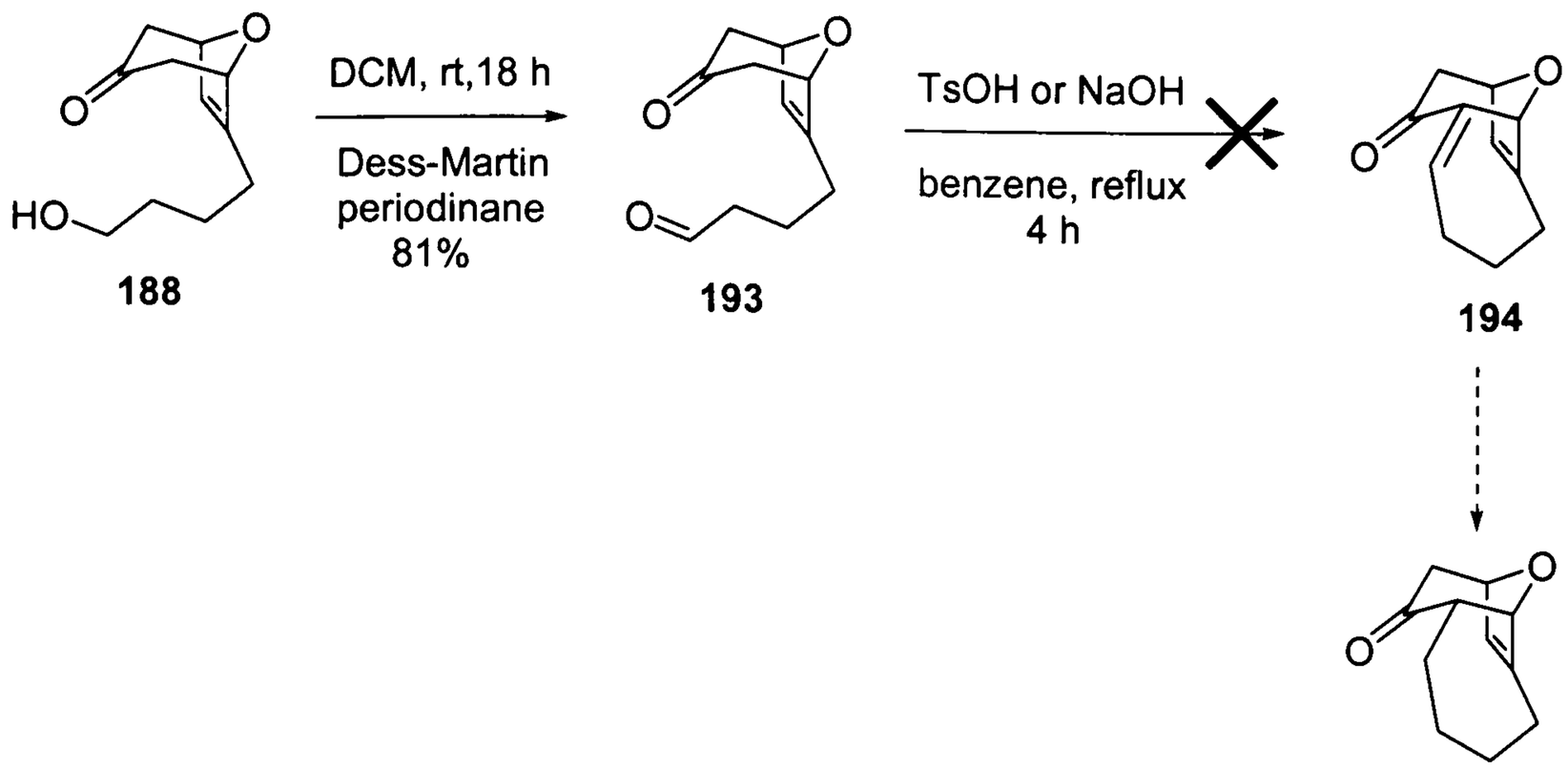


crystal structure of **195** from X-ray coordinates

Figure 5

Aldehyde **193** was also prepared from alcohol **188** using Dess-Martin periodinane in dichloromethane at room temperature (Scheme 73).[97] Aldehyde **193** was stable enough to be purified by column chromatography (2:1 ethyl acetate/60-80 petroleum ether). It was hoped that an intramolecular aldol condensation reaction of **193** would furnish vinylketone **194** that may subsequently be converted into the desired ketone **195** (Scheme 73).

In the event, attempted aldol condensation reaction of **193** under both acid and basic conditions proved disappointing. In both cases complete decomposition of the starting material was observed (Scheme 73).



Scheme 73

2.3.0 Conclusion

In conclusion, an investigation into a Type-II intramolecular [4 + 3] cycloaddition has shown the Favorskii rearrangement to be the major reaction pathway for oxyallyl cations generated from dihaloketones under classical conditions. The low yields of the Type-II cycloadduct have necessitated the development of an alternative approach to the same ring system based on intermolecular [4+3] cycloaddition followed by intramolecular enolate alkylation under thermodynamic conditions to close a seven membered ring.

CHAPTER 3

3.1.0 Reactions of alkylidenecarbenes

Alkylidenecarbenes (Figure 6) are neutral species containing a carbon atom with only six valence electrons. The carbenic carbon of alkylidenecarbenes is essentially sp hybridised, and can exist in two states, namely singlet and triplet. In the singlet ground state (lower in energy by 48 kcal/mol)[98,106] the two electrons are paired up in the nonbonding sp orbital (HOMO) which extends linearly as with alkynes and the p orbital (LUMO) is empty (Figure 1). The higher energy triplet state has one electron each in the nonbonding sp orbital and the p orbital.[99]As a result most alkylidenecarbenes react in the singlet ground state and evidence for this is found in the work by Gilbert and Ohira who reported that reaction of alkylidenecarbenes at stereogenic centres proceeded with retention of configuration (Scheme 74).[100,104, 106]

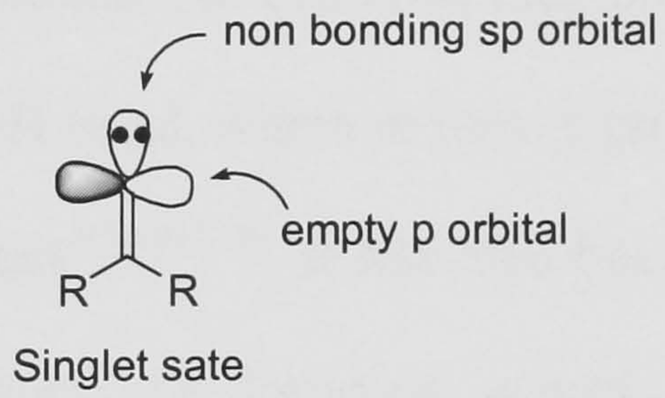
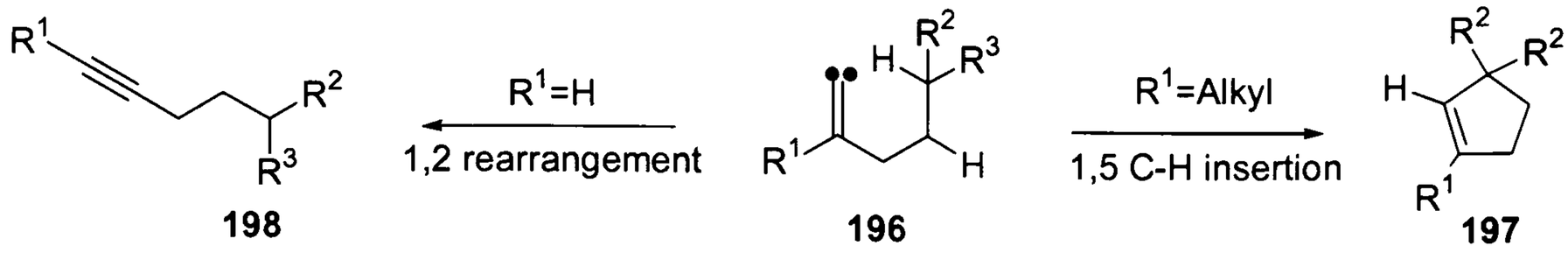


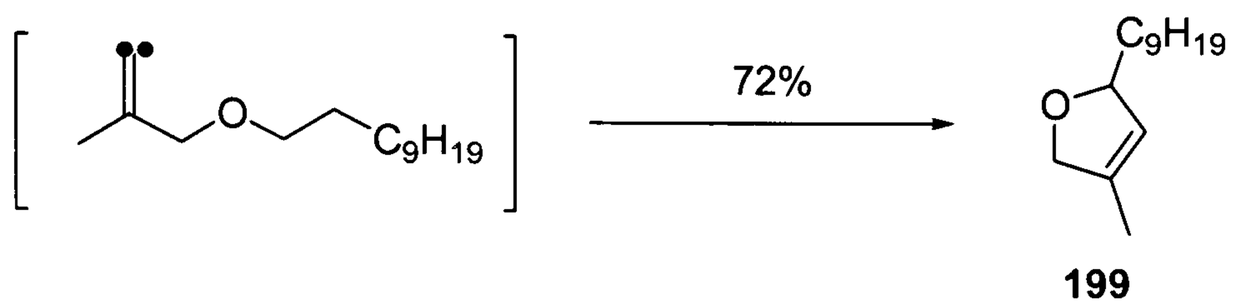
Figure 6

One characteristic reaction of alkylidenecarbenes involves a selective 1,5 C-H insertion into unactivated C-H bond five atoms away from the carbenic centre to give substituted or functionalised cyclopentene derivatives (Scheme 74).[101] Alkylidenecarbenes are also known to undergo 1,2-rearrangement with the formation of alkynes. Rearrangement dominates with R^1 = hydrogen, aryl, and halogen (Scheme 74).[98]



Scheme 74

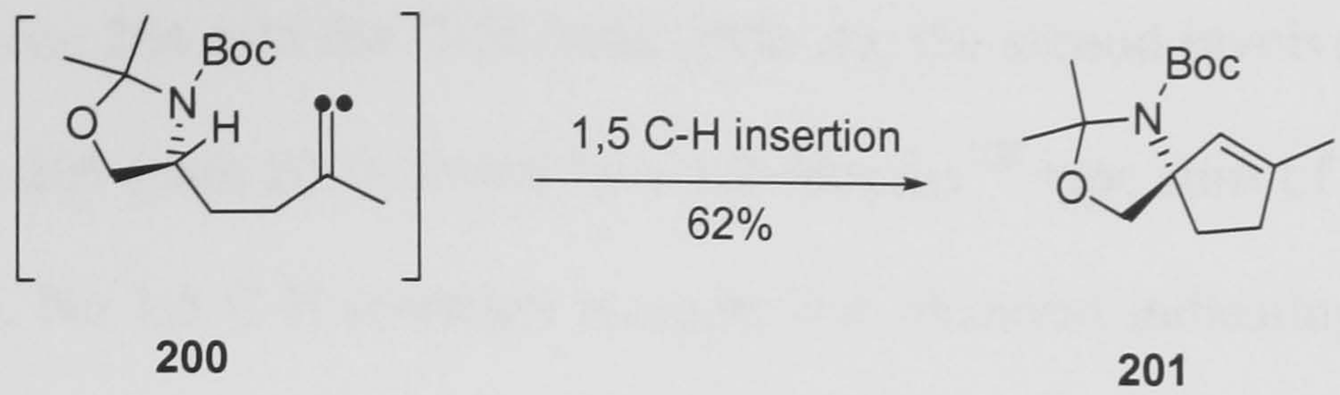
When a heteroatom is incorporated in the connecting chain, heterocycles such as dihydrofuran **199** can be formed in good yields (Scheme 75).[102]



Scheme 75

A common trend in the 1,5 C-H insertion of alkylidenecarbenes is their preference to insert into electron rich C-H bonds. For example, their preference to insert into tertiary C-H bond over secondary C-H bond, which in turn is greatly favoured over a primary C-H bond is well documented.[97b,103,104] It has also been reported that a heteroatom adjacent to the carbon where the insertion occurs increases the rate of C-H insertion.[100] In general, electron donating groups activate C-H bonds towards insertion and electron withdrawing groups deactivate.

For example, Hayes reported that insertion of alkylidenecarbene **200** gave substituted cyclopentene **201** (Scheme 76) and that 1,5 C-H insertion was preferred over 1,6 C-H insertion.[105]

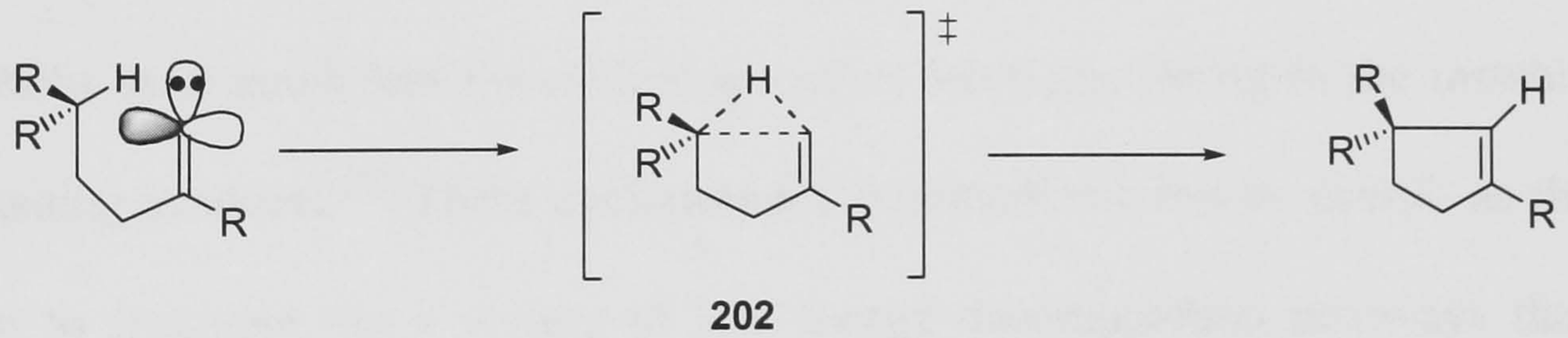


200 **201**

Scheme 76

Scheme 76 also highlights an additional attractive feature of alkylidenecarbene insertion reactions, that is quaternary centres are readily created from tertiary precursors with retention of configuration.[100,104,106]

The exact mechanism of the 1,5 C-H insertion reaction is unknown; however, it is believe that the reaction path does not involved any long-lived intermediates but rather a nonlinear interaction of the p-like empty orbital of the carbenic carbon atom and the σ electrons of the carbon-hydrogen leading to the formation of the complex **202** prior to 1,5-insertion (Scheme 77).[102]

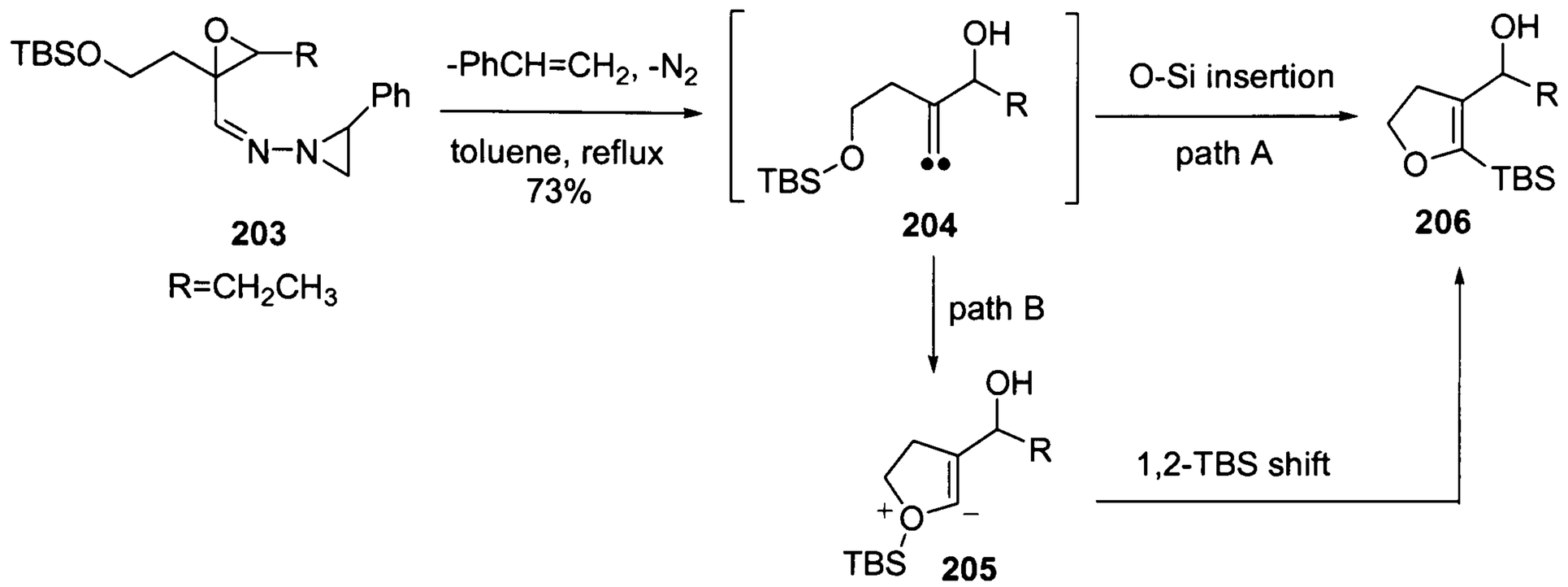


202

Scheme 77

Insertion into O-C, O-Si, and C=C bonds is well known to occur with various alkylidenecarbenes driven by their extreme electrophilicity. For example, thermal decomposition of α,β-epoxy-*N*-aziridinylimine **203** in refluxing toluene for 3 h gave dihydrofuran **206** in excellent yield (Scheme 78).[107] Formation of furan **206** was attributed to two possible reaction pathways. The first is a concerted 1,5 insertion of

alkylidenecarbene **204** into the O-Si bond (path A), the second involves formation of oxonium ylide **205** (path B) followed by a 1,2-Stevens[108] type shift of the TBS group to furnish **206**. No 1,5 C-H insertion reaction was observed indicating that 1,5 O-Si insertion of alkylidenecarbene **204** proceeds more rapidly than 1,5 C-H insertion (Scheme 78).



203

$R=CH_2CH_3$

204

205

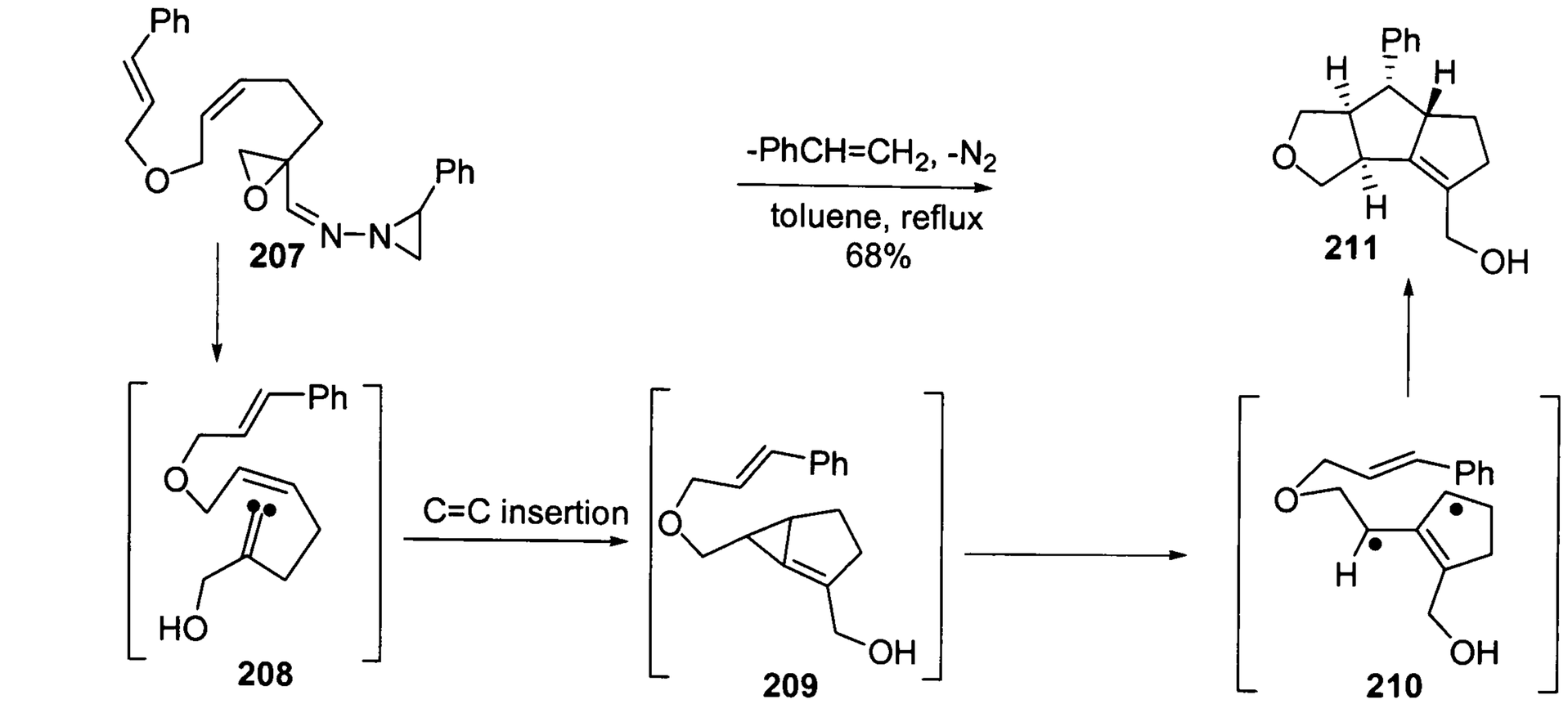
206

Scheme 78

While alkylidenecarbenes have been used most often for C-H insertion reactions, they have been used much less for cyclopropanation reactions, owing to the instability of the ensuing products.[109] These cyclopropane intermediates can be useful, as they are known to fragment via a variety of low energy decomposition pathways that may result in the formation of new structural frameworks with significant increase in molecular complexity.

For example, Lee reported formation of triquinane **211** through formation of alkylidenecarbene **208**. Derived alkylidenecarbene **208** in close proximity to an alkene functionality underwent a C=C insertion to form cyclopropane **209**. Fragmentation of

cyclopropane **209** gave diradical **210** which underwent a [2+3] cycloaddition reaction to form triquinane **211** (Scheme 79).[110]

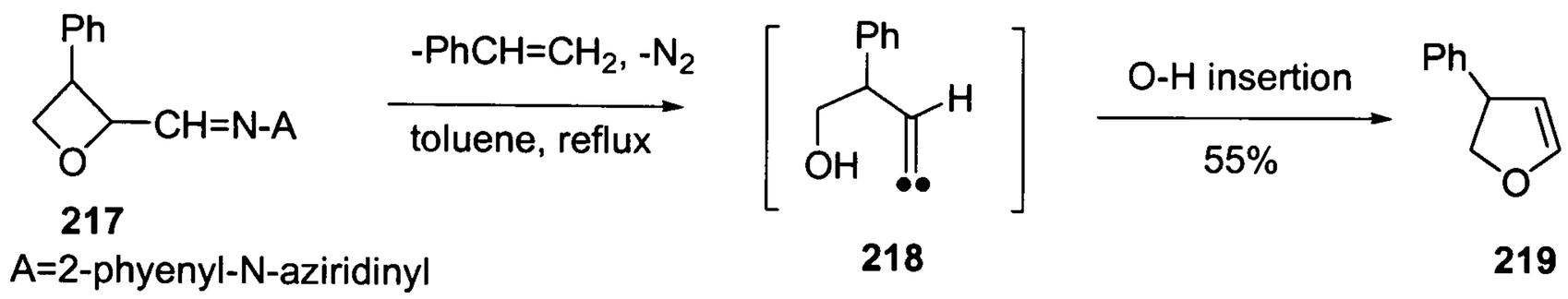


Scheme 79

Further example of the utility of cyclopropanes from alkylidenecarbenes can be found in the work reported by Feldman.[111] Treatment of iodonium salt **212** with lithium hexamethyldisilazide led to alkylidenecarbene **213** which underwent a rare aromatic

cycloaddition to methylenecyclopropane **214**. Fragmentation of cyclopropane **214** provided cycloheptatrienylidene **215** which rearranged to the tropoloisoquinoline alkaloid **216** upon treatment with KF on Al_2O_3 at -78 °C (Scheme 79).

Kim and co-workers examined the competition between 1,5 O-H insertion and a 1,2-H shift when oxetane **217** was refluxed in toluene for 8 h and dihydrofuran **219** (Scheme 80) was isolated in 55% yield, indicating that 1,5 O-H insertion of an alkylidenecarbene is favoured over a 1,2-H shift.[112]



217
A=2-phyenyl-N-aziridinyl

218

219

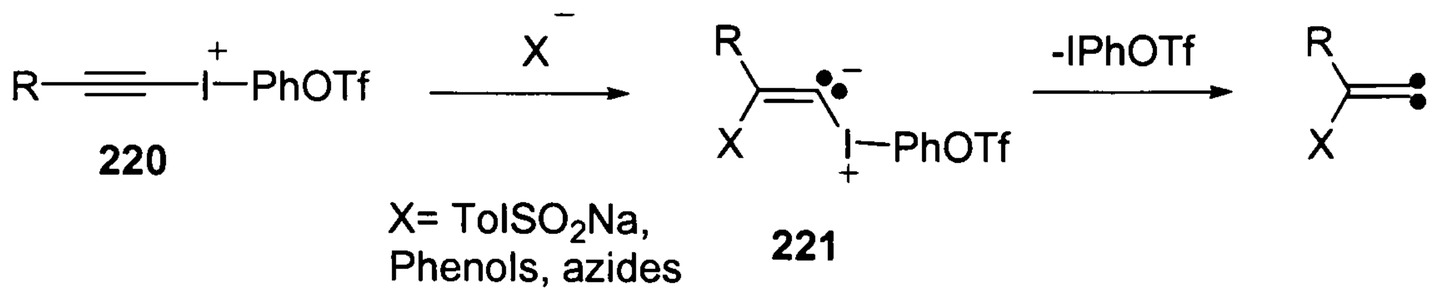
Scheme 80

3.1.1 Generating alkylidenecarbenes

A very popular source of akylidenecarbenes is the thermal decomposition of aziridinylimines in close analogy to the Eschenmoser fragmentation.[113] Thermal extrusion of styrene generates a diazo group with concomitant formation of C=C bond and a hydroxyl functional group from the ring opening of the oxirane ring. Nitrogen extrusion generates alkylidenecarbenes **204** and **218** (Schemes 78 and 80 respectively).

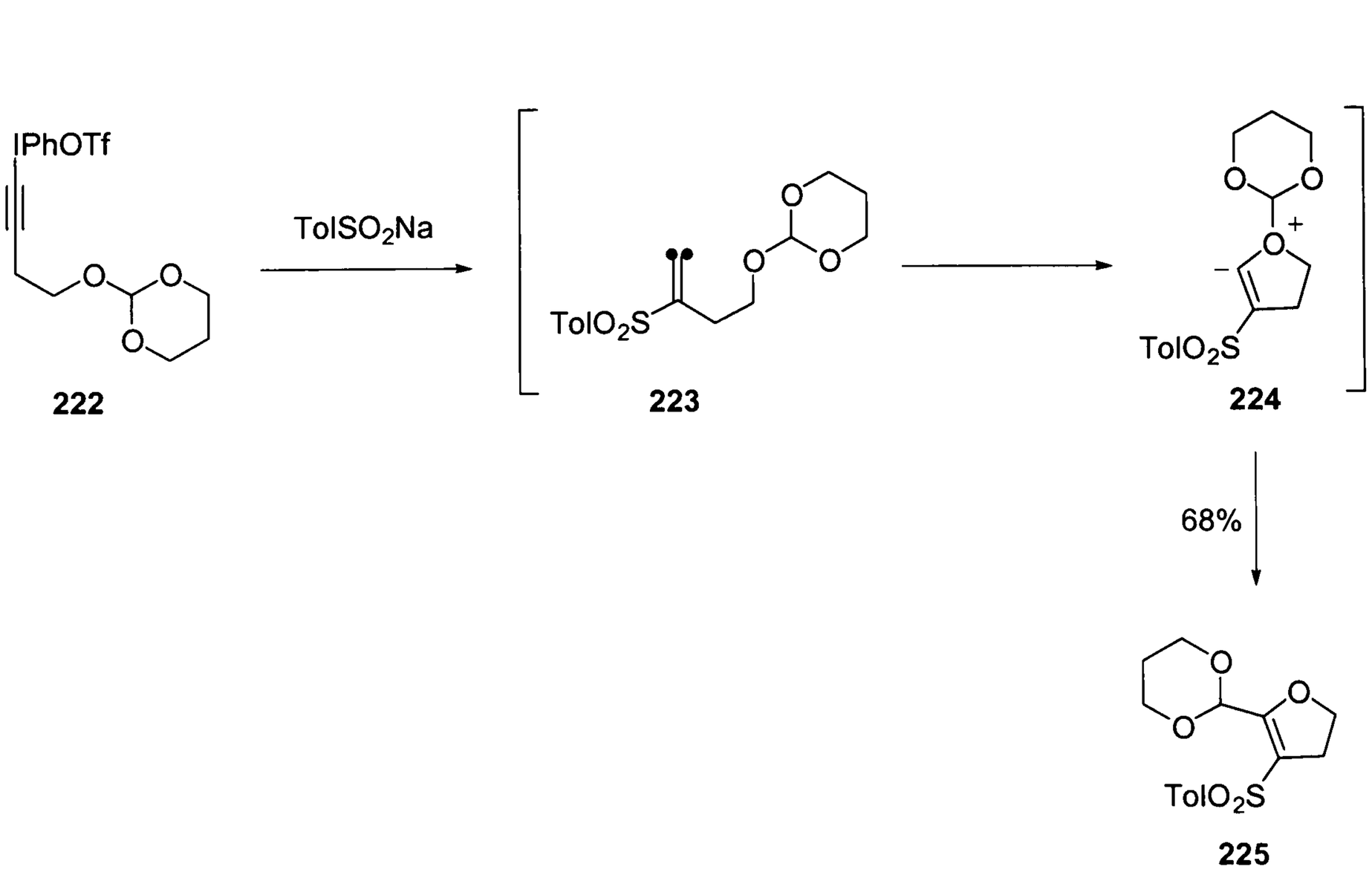
Another elegant method to generate alkylidenecarbenes is the addition of nucleophiles to akynyliodonium salts **220** to generate ylides **221** that loses aryl iodide to generate alkylidenecarbenes (Scheme 81). An advantage of this methodology is that it allows

formation of functionalised alkylidenecarbenes that are otherwise difficult to prepare.[114]



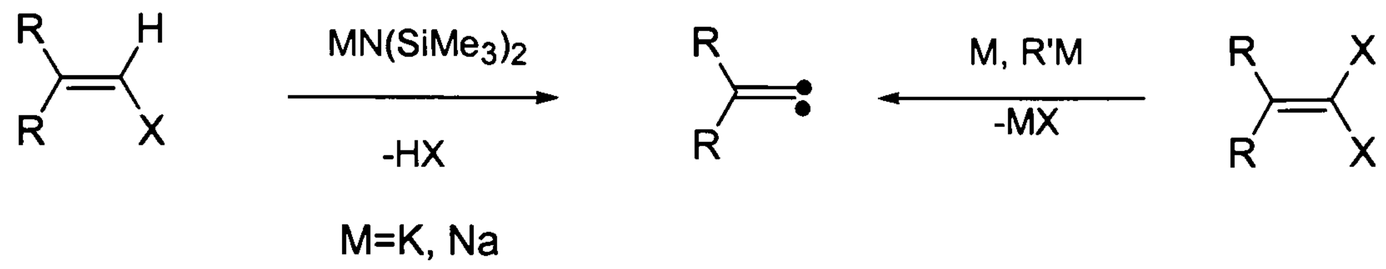
Scheme 81

For example, addition of sodium *p*-toluenesulfonate to alkynyliodonium salt **222** triggered a sequence of reactions which resulted in the formation of acetal **225** in good yield. Formation of functionalised alkylidenecarbene **223** prior to oxonium ylide **224** and subsequent 1,2-shift of the acetal functionality in **224** provided dihydrofuran **225** (Scheme 82).[115]



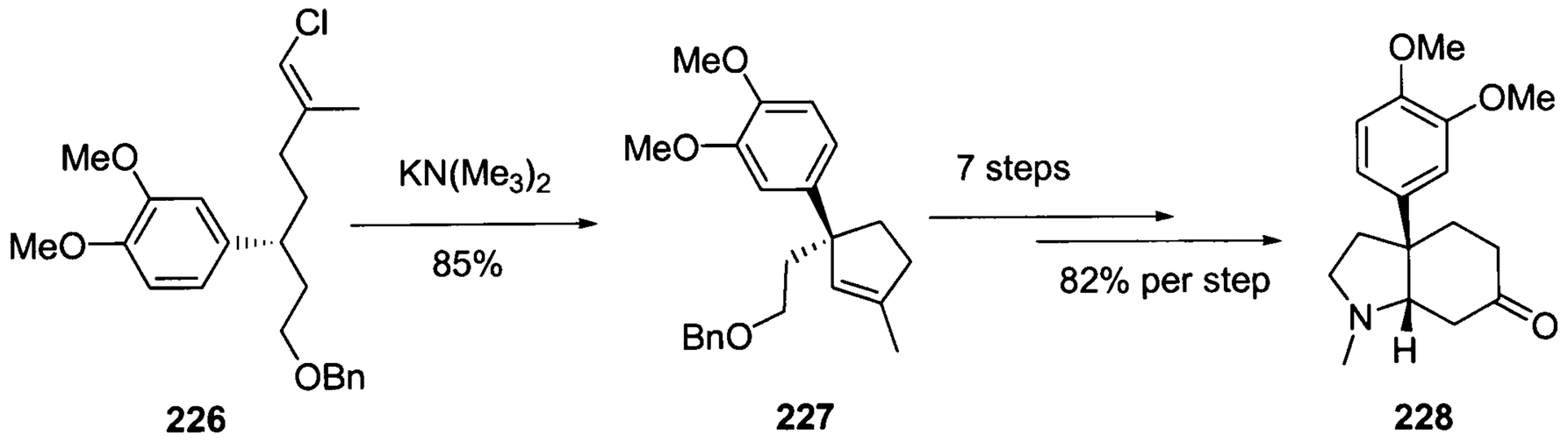
Scheme 82

Recently base induced elimination of vinyl halides[116] and Li/Br exchange in 1,1-dihaloalkenes[98] has found favour in alkylidenecarbene synthesis (Scheme 83).



Scheme 83

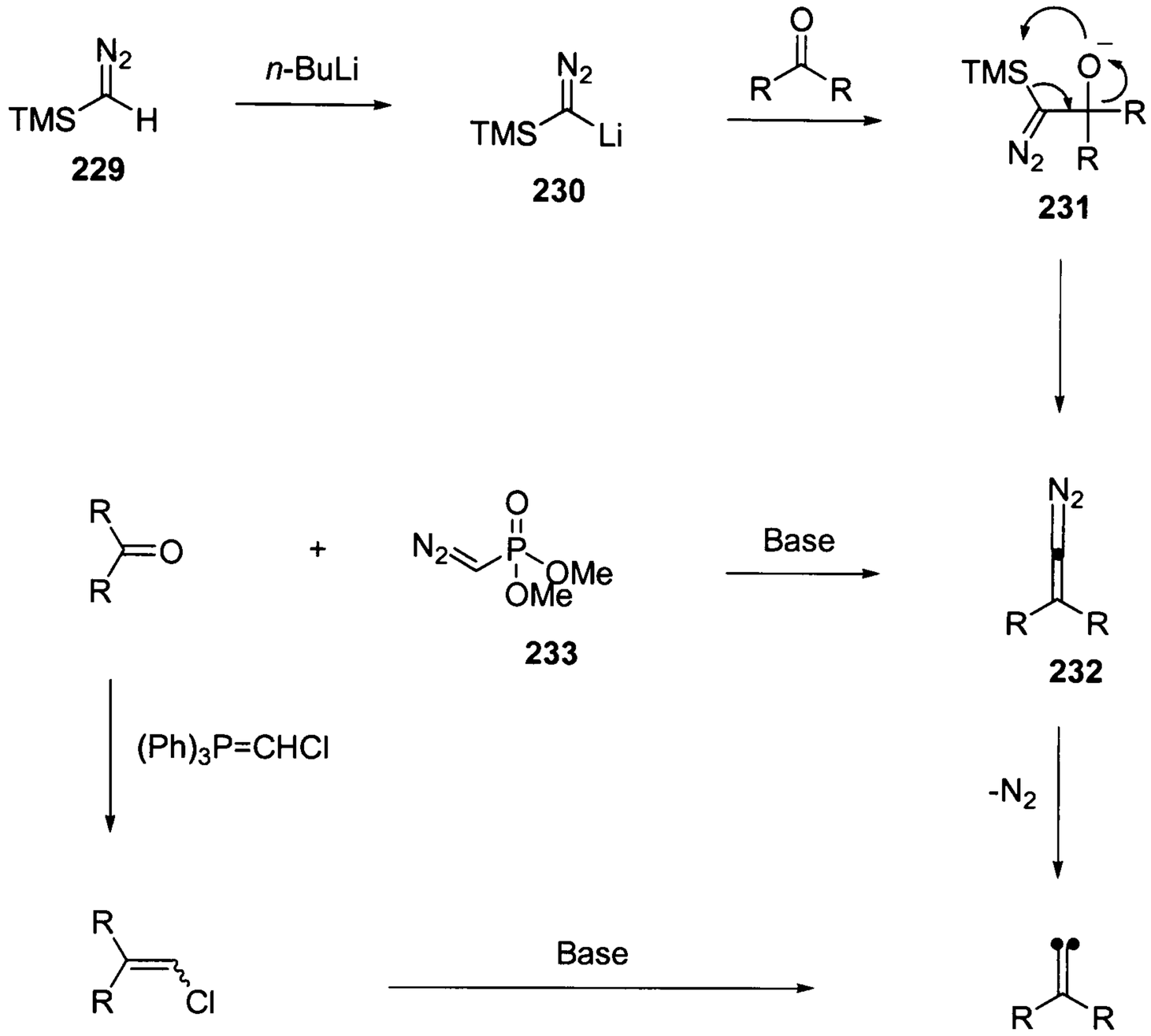
This methodology was applied by Taber to the synthesis of the alkaloid (-)-mesembrine **228**.[117] The key intermediate **227** was synthesised by base induced intramolecular alkylidenecarbene C-H insertion of vinyl chloride **226** to give the cyclopentene moiety of **227** with retention of stereochemistry. Compound **227** was converted into **228** in seven steps at an average yield of 82% per step (Scheme 84).



Scheme 84

A more general route to alkylidenecarbenes is the reaction of carbonyl compounds with commercially available lithio(trimethylsilyl)diazomethane **229** in a Peterson elimination (**231** to **232**)[118,119] or with dimethyl-diazomethylphosphonate **233** in the Horner-Emmons reaction (Scheme 85). Reactions with (chloromethyl)triphenylphosphonium chloride ylide are known to generate vinyl

chlorides **234** in a Wittig reaction, and base induced α-elimination of **234** leads to alkylidenecarbenes (Scheme 85).[120]

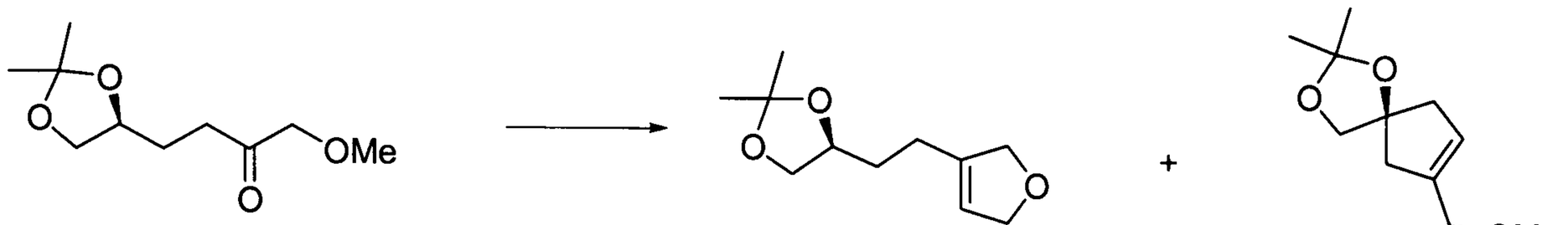


Scheme 85

The method of alkylidenecarbene generation can influence the selectivity of C-H insertion. It is known that carbenes generated via α-elimination are carbenoids in nature and their reactivity is dependent on the coordinating metal salts.[121] According to Taber, alkylidenecarbenes generated by α-elimination are in fact carbenoids, and that they are more selective in insertion reactions than the free alkylidenecarbenes generated by the Peterson elimination.[122]

For example, Taber showed that cyclisation of ketone **235** using trimethylsilyldiazomethane with methyl lithium as base only slightly favoured

compound **236** while it predominated in the chloromethylenation/elimination reaction using $(Ph)_3P{=}CHCl$ and $KN(SiMe_3)_2$ as base (Scheme 86). Furthermore, it appears that methyl C-H insertion is preferred over methine C-H insertion suggesting that the methyl oxygen is more activating towards insertion than the methine oxygen in this case (Scheme 86).[122]



235 **236** **237**

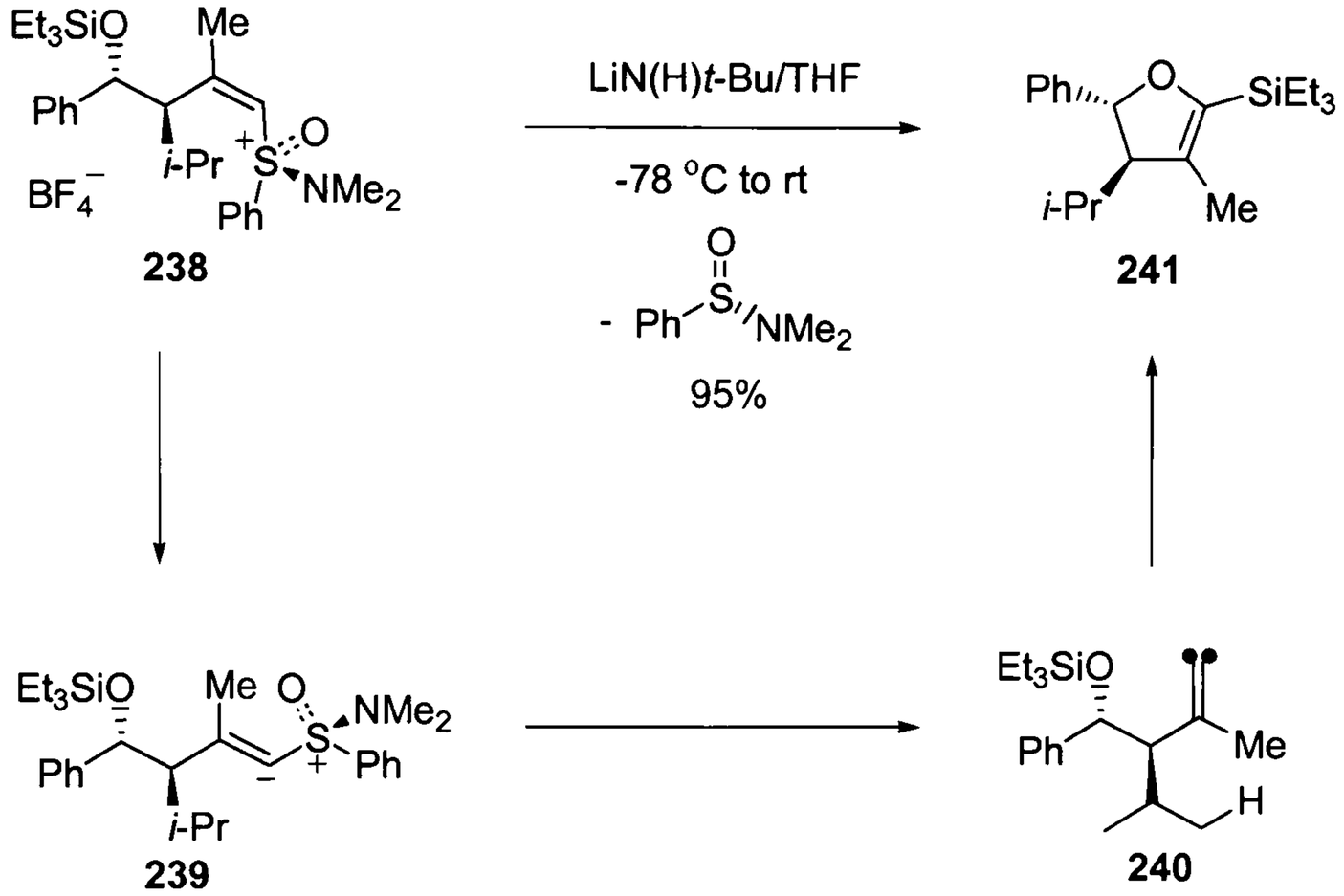
Method	Ratio 236:237	Yield
$TMSCH{=}N_2$/ MeLi	55:45	60%
a) $(Ph)_3P{=}CHCl$ b) $KN(SiMe_3)_2$	91:9	93%

Scheme 86

More recently, Gais reported the asymmetric synthesis of highly substituted mono- and bicyclic 2,3 dihydrofurans from chiral silyloxy alkylidenecarbenes.[123] For example, treatment of 1-alkenylaminosulfoxonium salt **238**[124] with lithium *tert*-butylamide in tetrahydrofuran first at -78 °C and then at room temperature afforded the enatio- and diastereomerically pure 2,3-dihydrofuran **241** in excellent yield (Scheme 87).

It was proposed that treatment of **238** with lithium amide at low temperatures affords alkylidenecarbene sulfoxonium ylide **239**, which then eliminates sulfinamide at higher temperatures with formation of alkylidenecarbene **240**. An intramolecular 1,5 O-Si insertion of **240** (insertion occurs either via a concerted or non-concerted pathway,

Scheme 78) resulted in the formation of dihydrofuran **241**. No derivatives of 1,2 Me-shift or 1,5 C-H insertion was observed, further evidence of the propensity of alkylidenecarbenes to undergo 1,5 O-Si insertion over 1,5 C-H insertion and 1,2-Me migration.

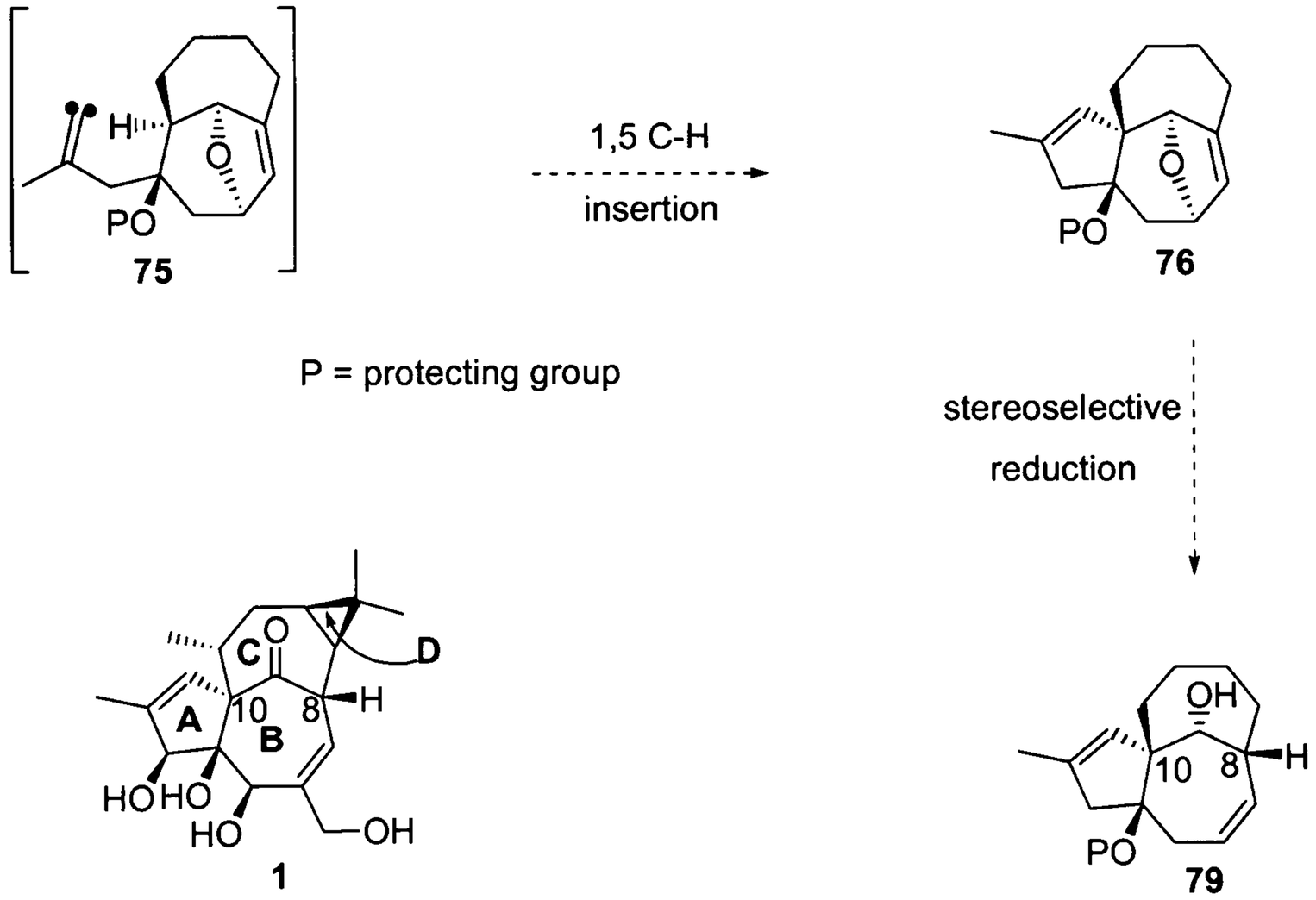


Scheme 87

In conclusion, alkylidenecarbenes are very useful intermediates in organic synthesis. Efficient methods for their generation are now available allowing rapid formation of alkynes via a 1,2 H-shift and the preparation of five-membered carbocyclic and heterocyclic rings systems through 1,5 insertion reactions. An attractive feature of the latter reaction is the preference to insert into tertiary over secondary C-H bonds with retention of configuration at the centre of insertion.

3.2.0 Results and Discussion II-Towards the A-ring of Ingenol

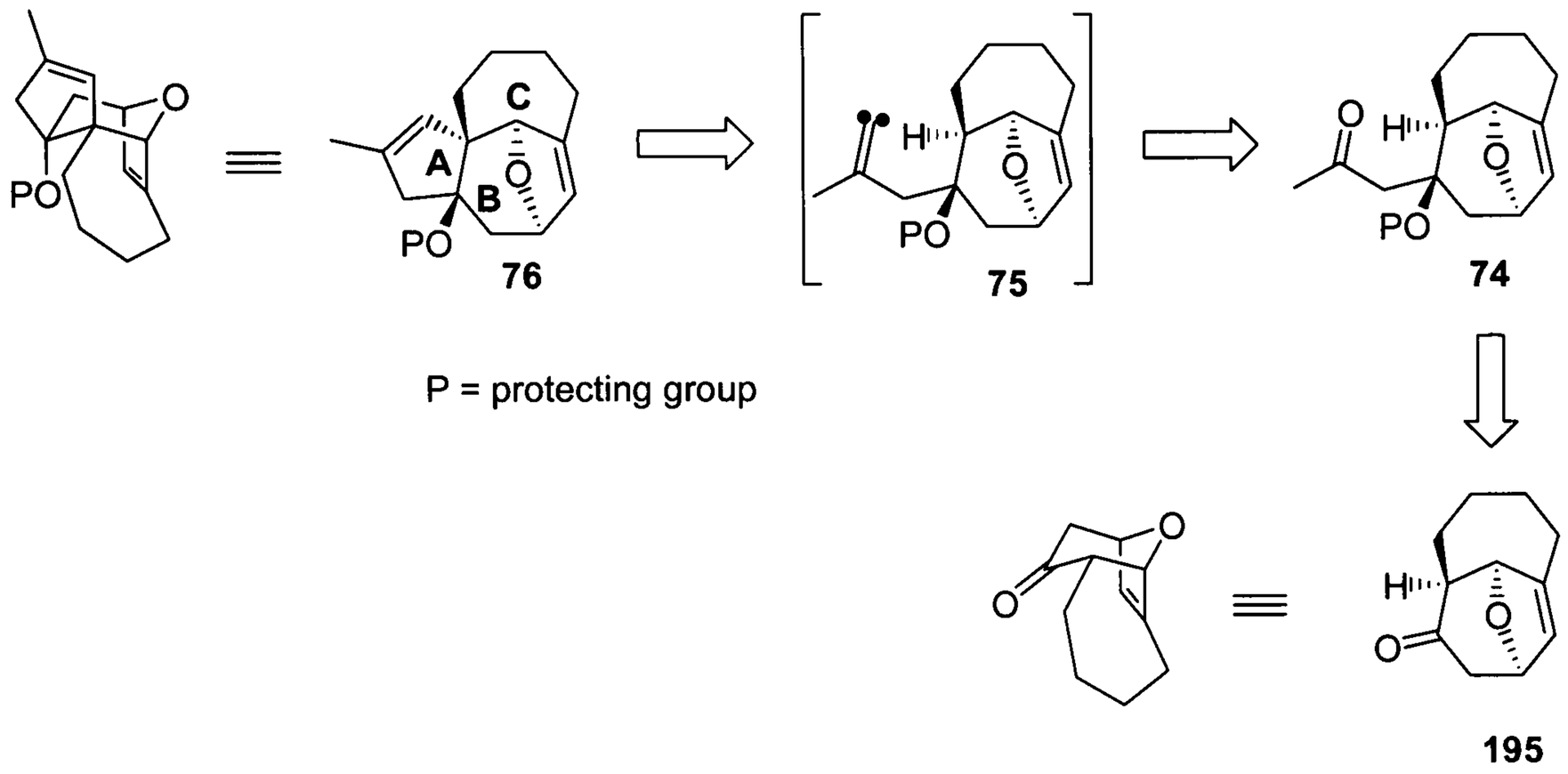
The aim of the project at this juncture was to embark on synthetic studies towards installation of the A-ring. This was deemed necessary in terms of the *trans* arrangement between C-8 and C-10 in the natural product ingenol (Scheme 88). To this end, compound **76** became the required synthetic target. Compound **76** could in theory be made possible by taking advantage of two characteristic features of alkylidenecarbene 1,5 C-H insertion reactions. Firstly, alkylidenecarbenes are known to insert selectively into tertiary over secondary C-H bonds, and secondly, the reaction occurs with retention of configuration at a stereocentre. With these considerations in mind, cyclisation of alkylidenecarbene **75** should render compound **76** which in turn could be exploited to the *trans* ring junction of **79** (Scheme 88).



Scheme 88

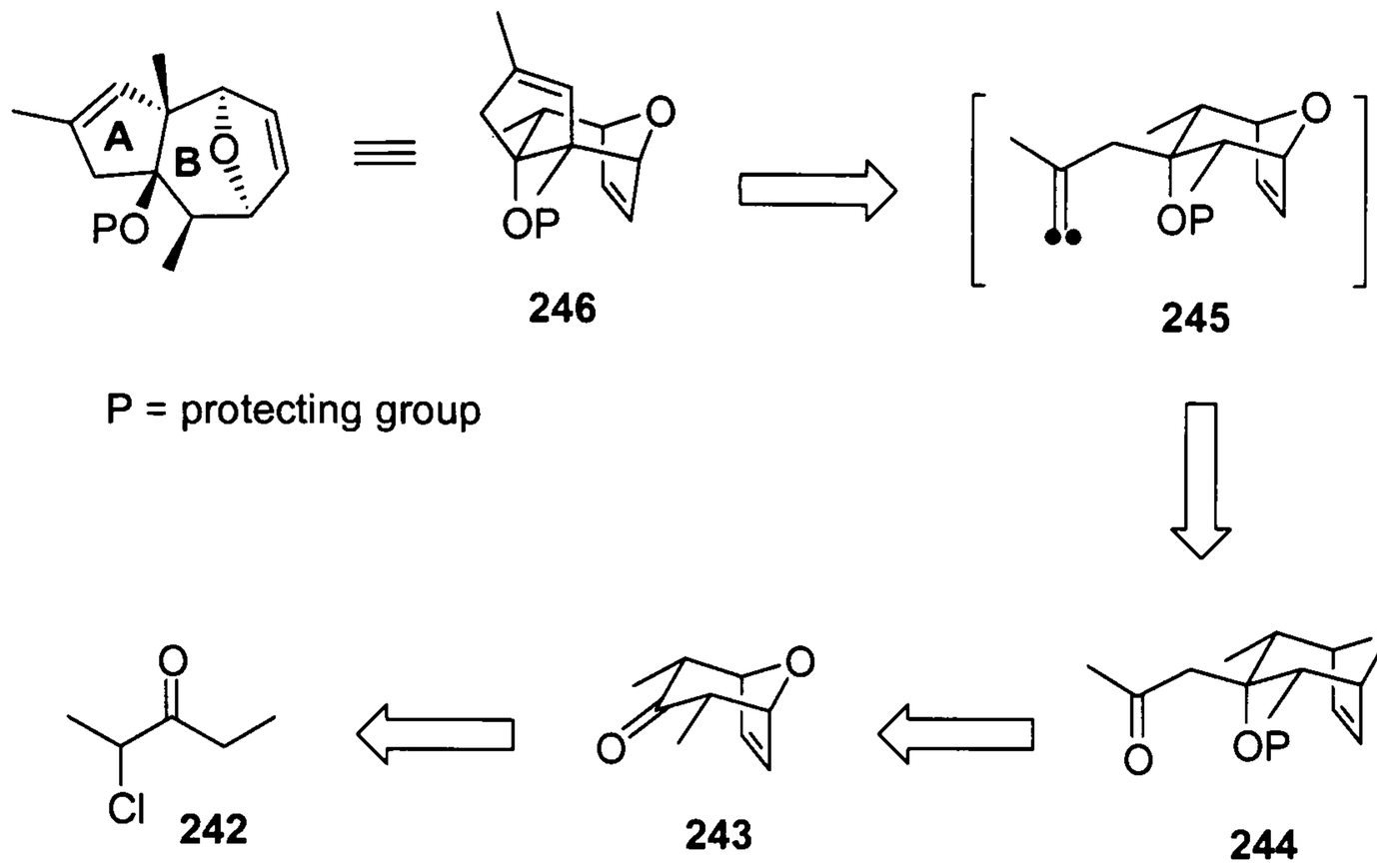
3.2.1 Retrosynthetic analysis for compound 76

A retrosynthetic analysis of compound **76** is outlined in Scheme 89. It was envisioned that a selective base-promoted 1,5 C-H insertion reaction of alkylidenecarbene **75** should render desired tetracyclic ether **76** (Scheme 89). Alkylidenecarbene **75** may be prepared from ketone **74** using a suitable method such as those outlined in Scheme 85. Tricyclicketone **74** may be synthesised by a face selective aldol reaction between ketone **195** and the enolate of acetone, following protection of the ensuing alcohol.



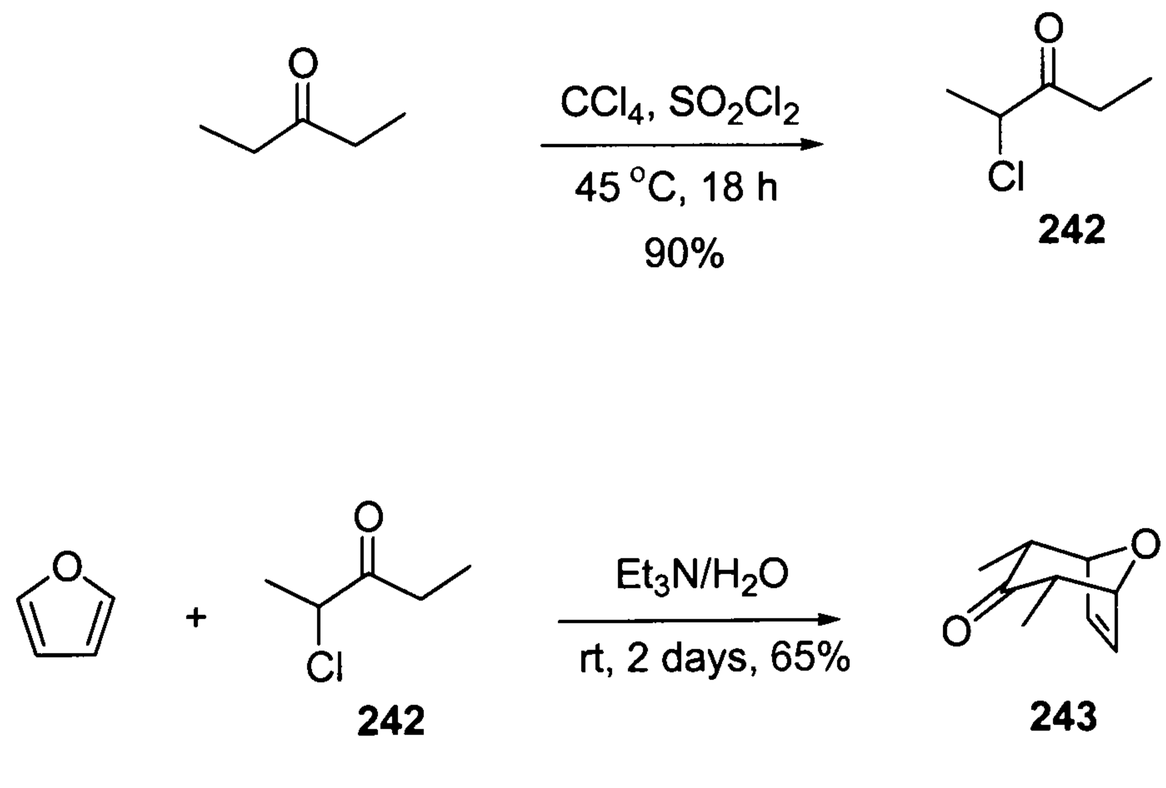
Scheme 89

A representative study of the synthetic strategy envisioned was first carried out. Towards this end, the readily available oxabicyclic ketone **243** was thought to be a good model for ketone **195**. Synthesis of cis-fused perhydrozulene **246** could be realised from ketone **243** using the same methodology envisioned for the synthesis of **76** from **195** (Scheme 89). An intermolecular [4+3] cycloaddition reaction between furan and 2-chloropentan-3-one **242** should deliver ketone **243** (Scheme 90).



Scheme 90

The reaction between 3-pentanone and sulfuryl chloride in carbon tetrachloride at 45 °C proceeded without incident. The reaction was concentrated at atmospheric pressure after 18 h to give **242** as a yellow oil that was sufficiently pure to be used in the next step without further purification (Scheme 91). [125]

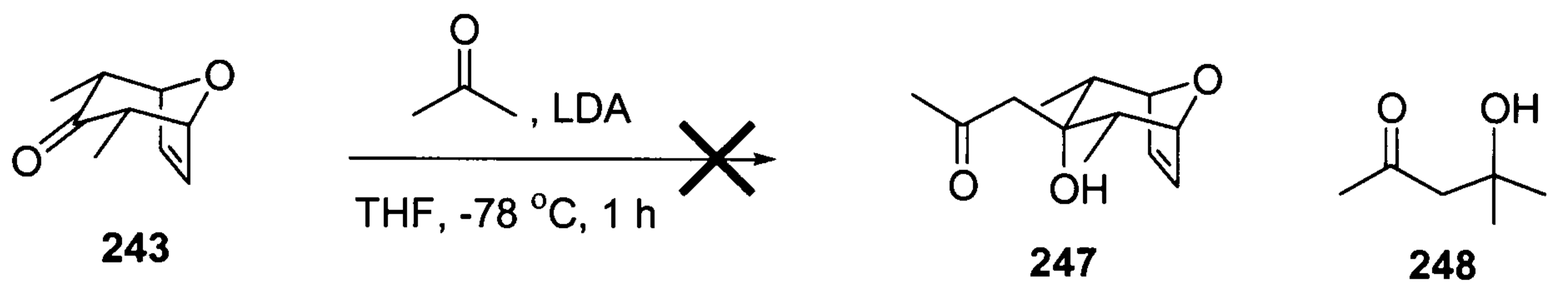


Scheme 91

An intermolecular [4+3] cycloaddition reaction between furan and 2-chloropentan-3-one proceeded uneventfully at room temperature for 2 days, delivering known oxabicyclic ketone **243** in good yield (Scheme 91). Maximum yield of **243** is obtained

by re-submitting the mixture after 2 days to the reaction conditions based on 40% un-reacted starting 2-chloropentan-3-one (Scheme 91).[125]

A number of methods were investigated to achieve the formal aldol reaction between acetone and oxabicyclic ketone **243** (Table 3). Generation of acetone enolate by deprotonation with lithium diisopropylamide followed by treatment with ketone **243** gave recovered starting material and cross aldol product **248** (Scheme 92 and entry 1, Table 3).[126] Reaction of ketone **243** with 2-(trimethylsiloxy) propene (Table 3, entry 2), or isopropenyl acetate (Table 3, entry 3) in the presence of a suitable Lewis acid all resulted in the recovery of starting material.[127]



243 **247** **248**

Scheme 92

The reaction of ketone **243** and isopropenyl acetate in the presence of diethylaluminium chloride (Table 3, entry 4) led to destruction of starting material. Purification of the crude reaction by column chromatography (5:1 60-80 petroleum ether/hexane) gave trace amounts of the axial alcohol **249**. Formation of alcohol **249** may be attributed to hydroalumination of the carbonyl functionality in ketone **243** from the more accessible *exo* face. The stereochemistry of known alcohol **249** was consistent with that reported in the literature.[151]

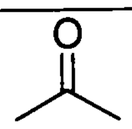
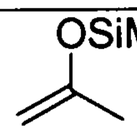
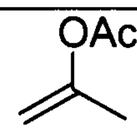
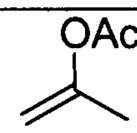
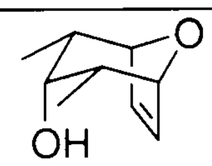
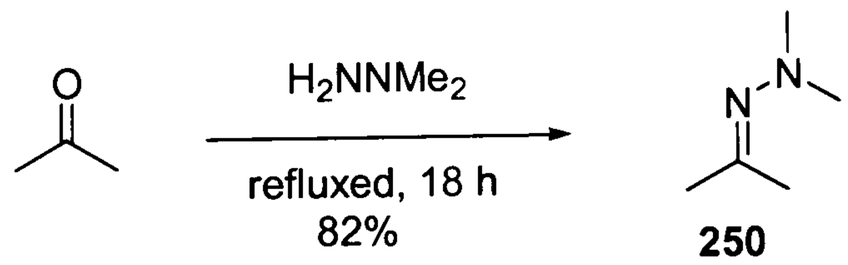
entry	ketone	conditions	product (**247**)
1	**243**	 LDA, THF, -78 °C, 1 h	No reaction
2	**243**	 $TiCl_4$, DCM, 0 °C, 2 h	No reaction
3	**243**	 Et_2AlOEt, DCM, 0 °C, 1.5 h	No reaction
4	**243**	 Et_2AlCl, DCM, -78 °C, 2 h	 **249**

Table 3

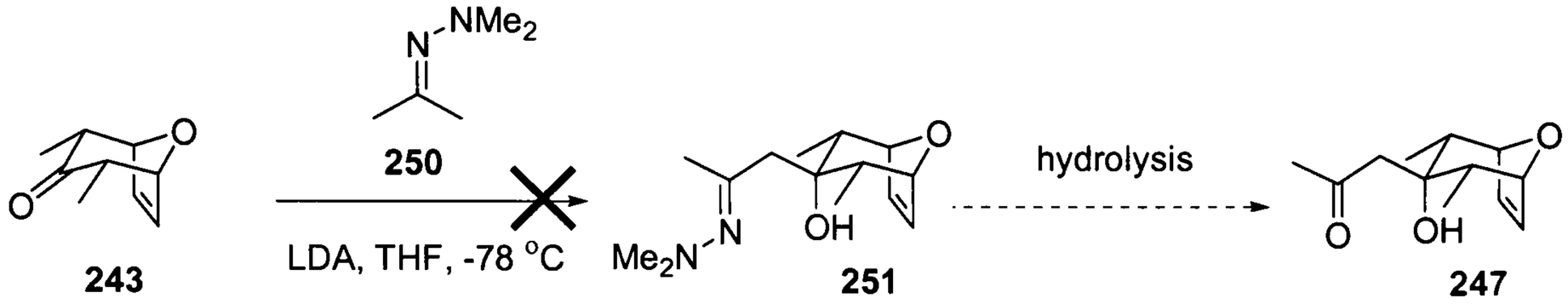
The results in Table 3 prompted consideration of alternative strategies based on addition of suitable nucleophilic reagents that could subsequently be converted into an alkylidenecarbene precursor such as a vinyl halide. With this in mind, a variety of organometallic precursors were synthesised.

The reaction between acetone and *N,N*-dimethylhydrazine was effected by refluxing for 18 h using a Dean-Stark apparatus. The crude reaction was purified by distillation over calcium hydride at atmospheric pressure collecting the fraction between 92-95 °C to provide desired imine **250** in excellent yield (Scheme 93).[128]



Scheme 93

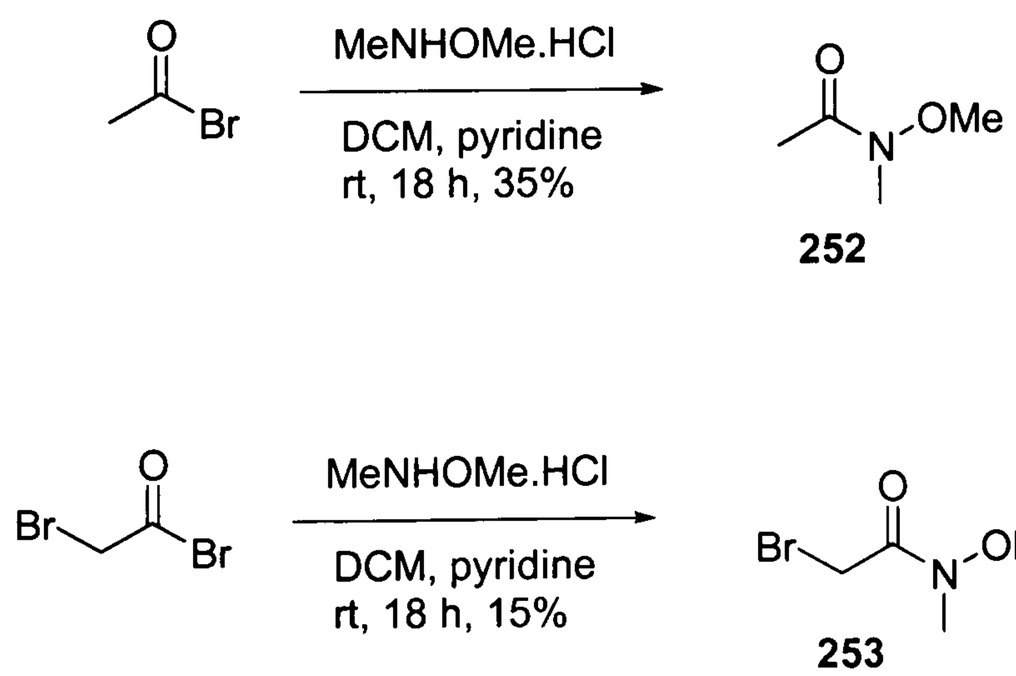
The reaction of ketone **243** and metalated hydrazone from **250** gave none of the desired β-hydroxy hydrazone **251**. The reaction resulted in the recovery of starting ketone **243** (Scheme 94).[129]



Scheme 94

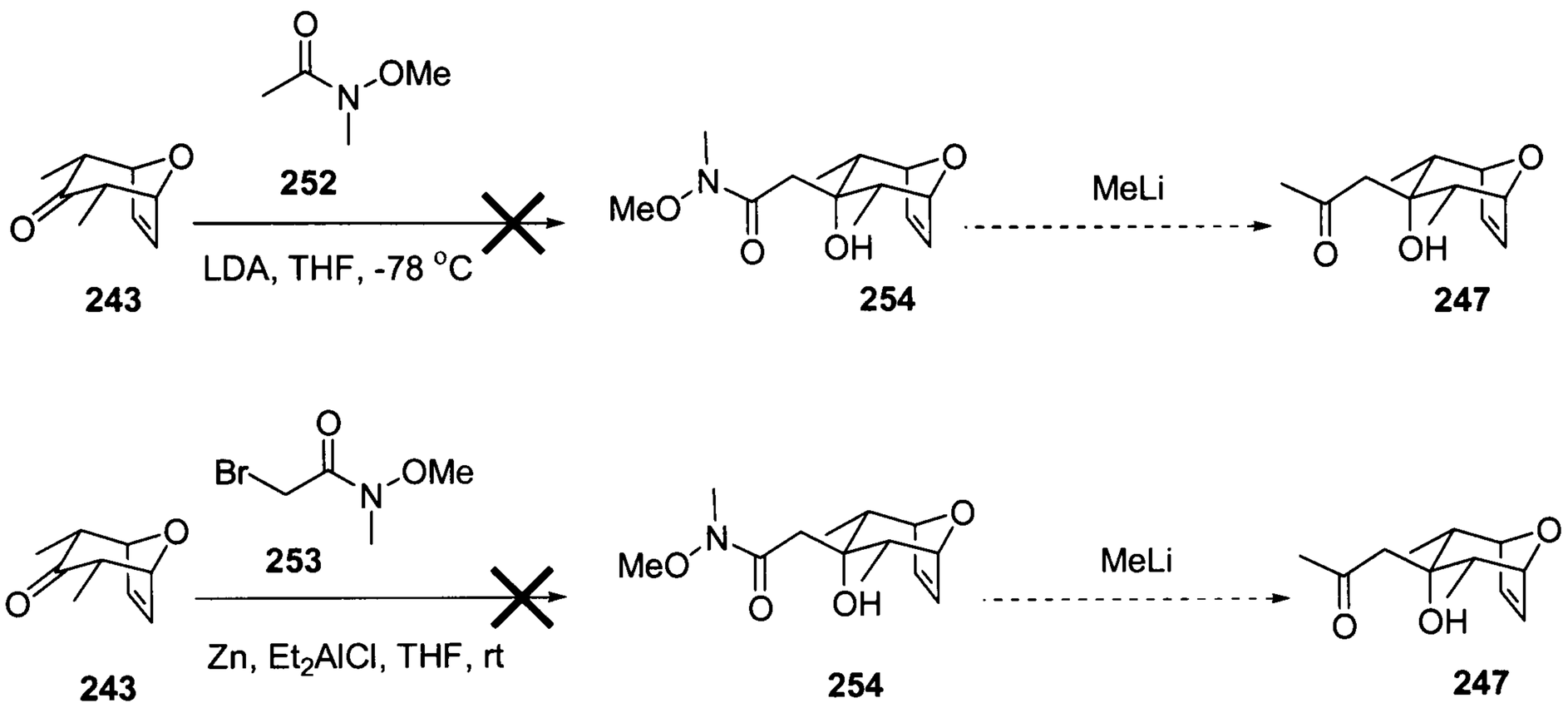
The reaction of acetyl bromide and *N,O*-dimethylhydroxylamine hydrochloride in the presence of pyridine in dichloromethane at room temperature gave satisfactory yield of amide **252** (Scheme 95).[128]

Attempted reaction of bromoacetyl bromide with *N,O*-dimethylhydroxyamine hydrochloride under same conditions for amide **252** was disappointing; bromoamide **253** could only be obtained in 15% yield. Both compound **252** and **253** were sufficiently pure and used without further purification (Scheme 92).[130]



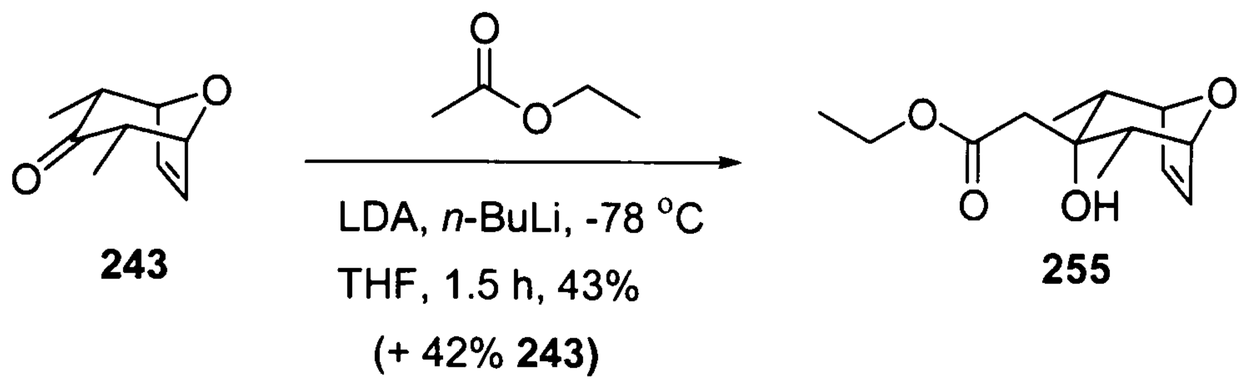
Scheme 95

Attempted reactions between **243** and the enolate of amide **252** or the aluminium enolate from bromide **253** in a Reformatsky type reaction were all frustrated by the recovery of starting ketone **243** (Scheme 96).[131] No dimeric condensation product from **252** or **253** was observed, suggesting that the organometallic intermediate from **252** and **253** may not have been formed or ketone **243** is simply not reactive under these reaction conditions (Scheme 96).[132]



Scheme 96

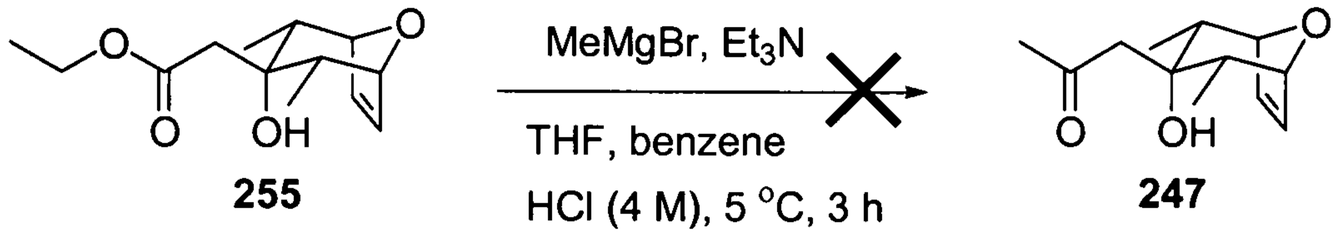
Kikkawa reported a convenient method of converting readily available esters into ketones.[133] To that end, it was pleasing to observed that attempted addition of the enolate of ethyl acetate to ketone **243** afforded ester **255** as the only product in the reaction, albeit in moderate yield (Scheme 97). In addition 42% of starting ketone **243** was recovered. It is assumed that nucleophilic addition to **243** occurred from the less hindered *exo* face leading to formation of the *endo* alcohol **255** (Scheme 97).



243 **255**

Scheme 97

Attempted synthesis of β-hydroxyketone **247** from ester **255** under Kikkawa's conditions was thwarted by the destruction of starting material. ^{1}H-NMR of the crude reaction showed formation of desired alcohol **247** in only trace amounts (Scheme 98).[131]



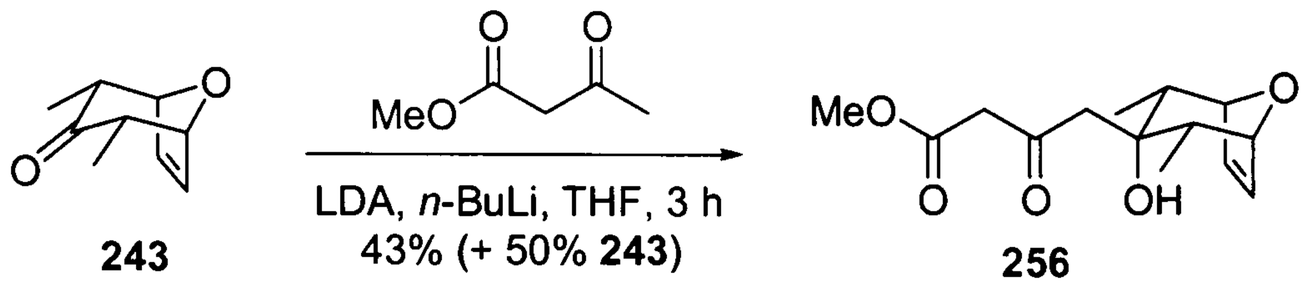
255 **247**

Scheme 98

At this point, the reaction in Scheme 97 was the first successful direct enolate addition to [3.2.1] oxabicyclic ketone **243**. Given these encouraging results, a more reactive enolate in the form of the dianion of methyl acetoacetate was reacted with ketone **243**.[134]

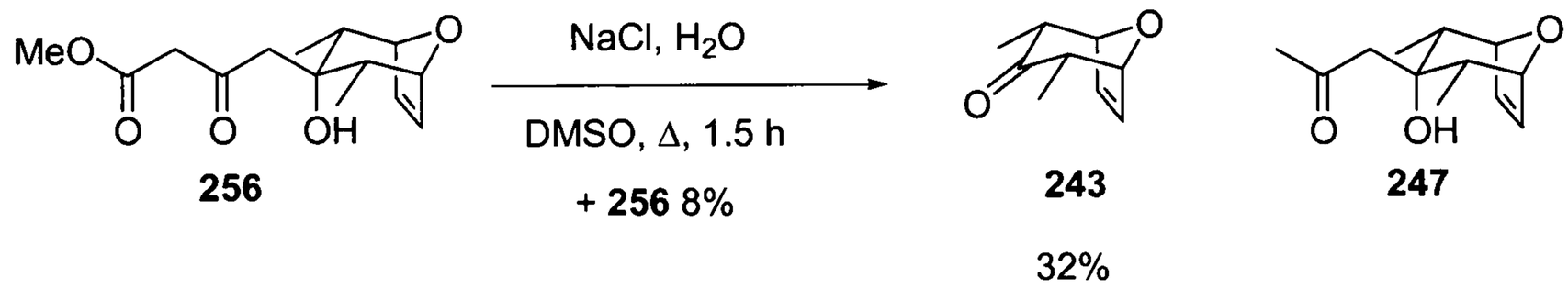
In the event, direct addition using four equivalents of *in situ* generated dienolate of methyl acetoacetate to ketone **243** at -78 °C in tetrahydrofuran resulted in the formation of β-keto ester **256** as the only product in satisfactory yield. In addition 50% of starting material **243** was recovered (Scheme 99). It was assumed that the hydroxyl

group in **256** would be axially orientated following addition from the less sterically hindered *exo* face of the carbonyl functionality in **243** (Scheme 99)



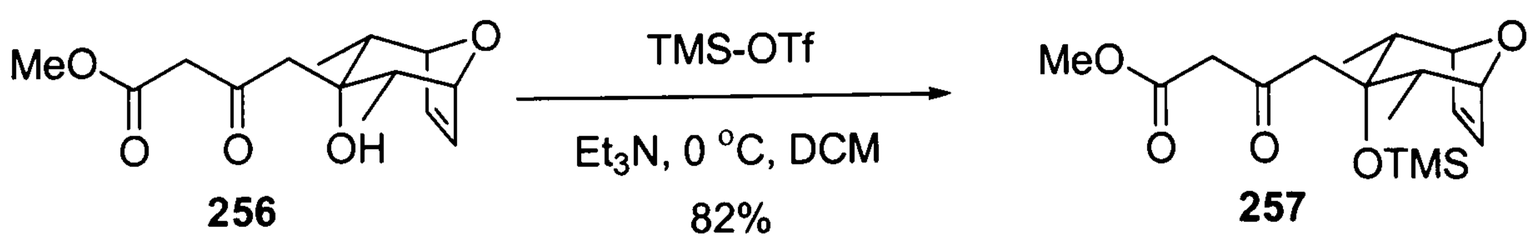
Scheme 99

Interestingly, attempted decarboxylation of ester **256** prior to protection using sodium chloride in wet dimethylformamide at elevated temperatures, resulted in the formation of the retro-aldol product **243** in 32% yield, followed by 8% of starting material. Formation of desired product **247** was not observed in the reaction (Scheme 100).[86]



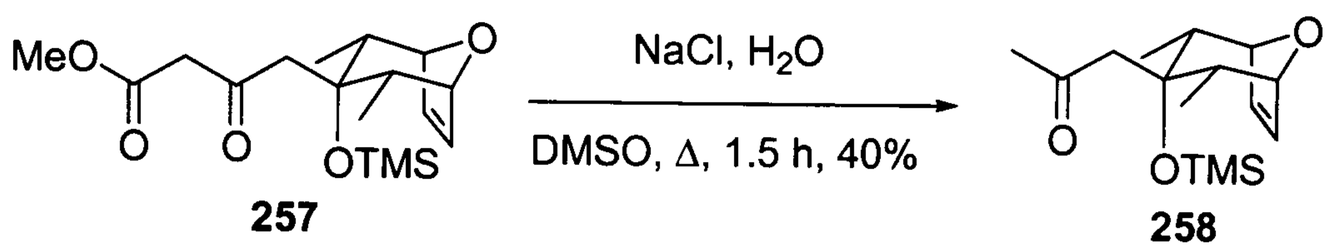
Scheme 100

Gratifyingly, alcohol **256** could readily be protected using trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C. Under these conditions protected β-keto ester **257** was obtained in excellent yield (Scheme 101).



Scheme 101

With compound **257** in hand, decarboxylation was effected by using sodium chloride in a heated mixture of dimethylformamide and water. Under these conditions required silylated ketone **258** was obtained in moderate yield (scheme 102). Compound **258** was isolated as a colourless oil following purification of the crude reaction by column chromatography (4:1 hexane/ethyl acetate). Surprisingly, decarboxylation of **257** yielded no starting material despite the moderate yield of product **258**.[86]

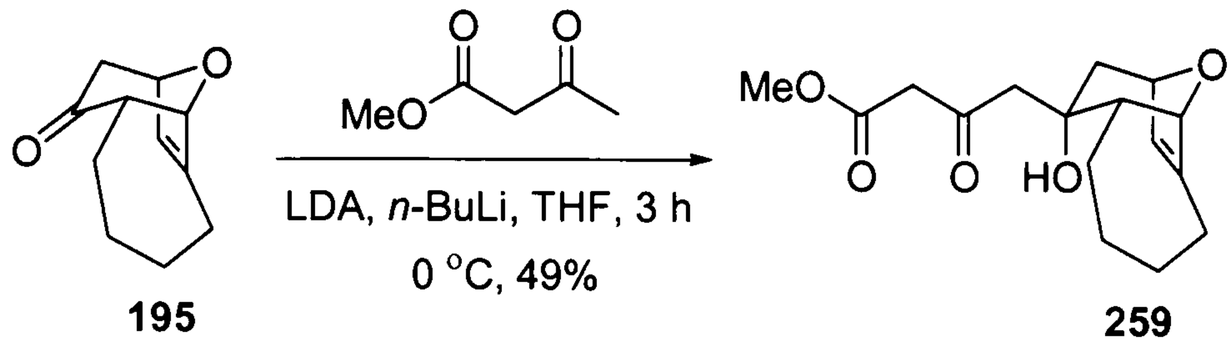


257 **258**

Scheme 102

Given the above encouraging results, tricyclic ketone **195** was taken through an identical sequence of reactions as ketone **243**.

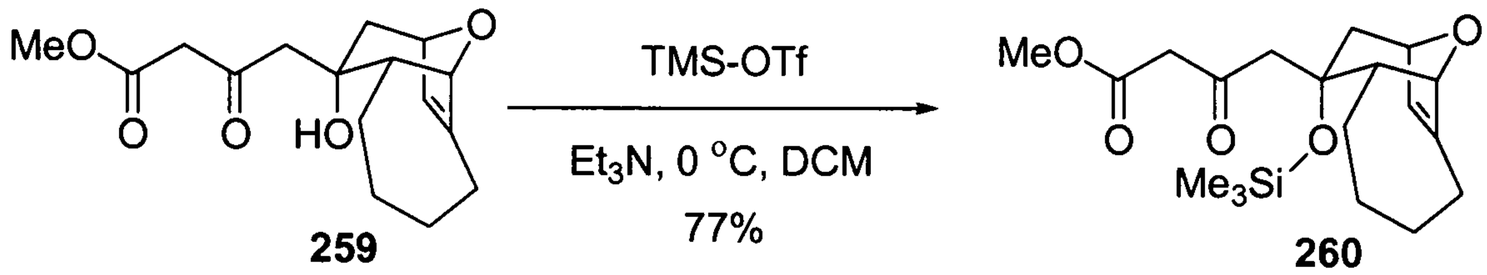
In the event, addition of the dianion of methylacetoacetate to oxatricyclic ketone **195** was effected in tetrahydrofuran at 0 °C. The crude reaction was purified by column chromatography (2:1 hexane/ethyl acetate) to afford compound **259** as a colourless oil in 49% yield (scheme 103). As in the nucleophilic addition to ketone **243** (Scheme 99), the stereochemical outcome of the reaction was predicted on the basis of steric bias provided by the rigid template of the oxabicyclic frame work. However, unlike the reaction of compound **243** only trace amounts of the starting material was isolated in contaminant amounts of methyl acetoacetate (Scheme 103).



195 259

Scheme 103

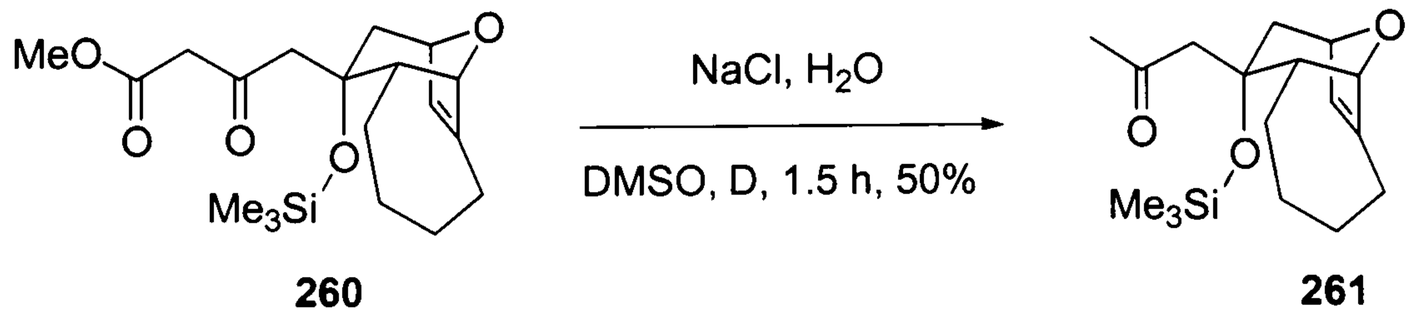
Protection of alcohol **259** was accomplished uneventfully using trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C (Scheme 104). Under these conditions, the required protected ester **260** was isolated as a colourless oil in 77% yield following purification of the crude reaction by column chromatography (2:1 hexane/ethyl acetate).



259 260

Scheme 104

The synthesis of ketone **261** was achieved by decarboxylation of ester **260** using sodium chloride in wet dimethylformamide at elevated temperatures. Under these standard conditions protected β-hydroxyketone **261** was isolated in satisfactory yield (Scheme 105).[86] No starting material was recovered under the reaction conditions.

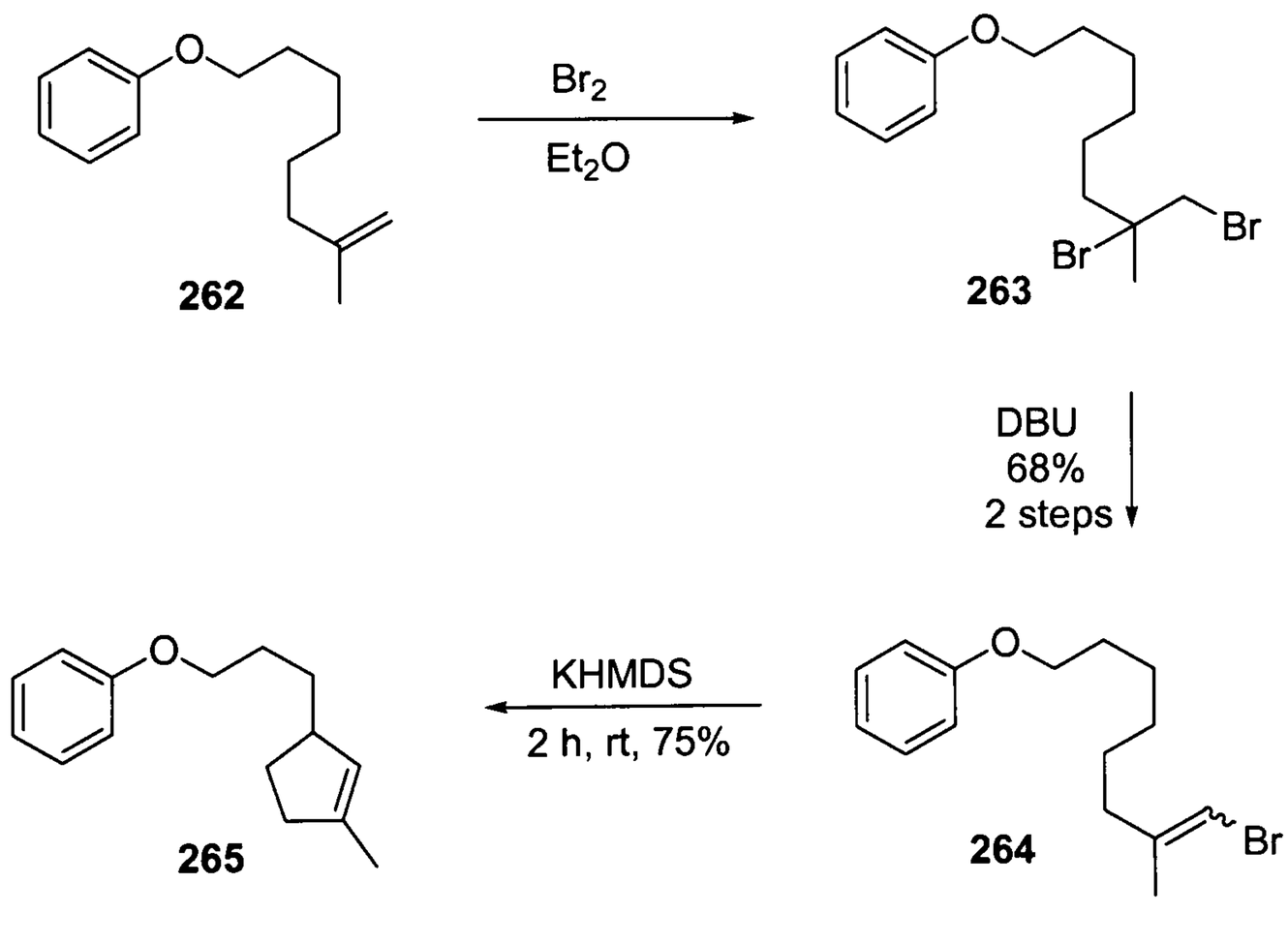


260 261

Scheme 105

Although the enolate addition steps (schemes 99 and 103) were successful, the yields were low, and decarboxylation of esters **257** and **260** only gave moderate yields of ketones **258** and **261** (Schemes 102 and 105 respectively). Hence, more reactive nucleophiles in the form of Grignard reagents were pursued.

Taber reported a bromination-dehydrobromination strategy for the conversion of terminal alkenes to vinylbromides. For example, Taber reported that bromination of alkene **262** gave dibromide **263**. Dehydrobromination of compound **263** using 1,8 diazabicyclo[5.4.0]undec-7-ene afforded vinyl bromide **264**. Treatment of **264** with three equivalent of potassium bis (trimethylsilyl)amide in *p*-dioxane at room temperature effected an intramolecular 1,5 C-H insertion reaction to cyclopentene **265** in good yield (Scheme 106). [135]

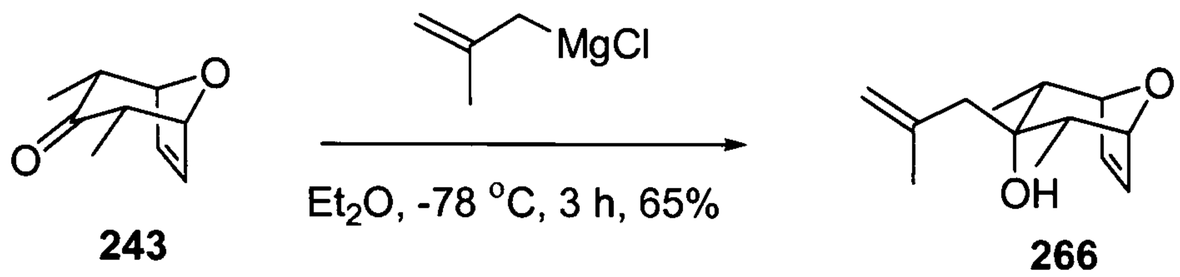


262 **263** **264** **265**

Scheme 106

Towards this end, reaction of 2-methylallylmagnesium chloride with model ketone **243** was pursued. In the event, addition of the Grignard reagent to ketone **243** in

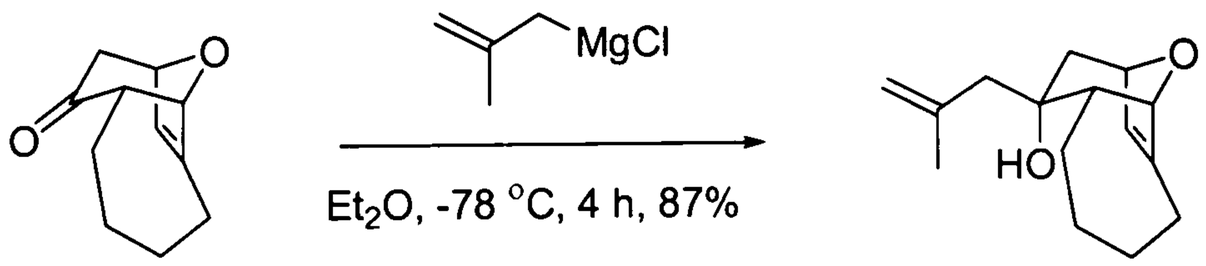
diethyl ether at -78 °C proceeded without incident to give a single diastereomeric alcohol believed to be compound **266** in good yield (Scheme 107).[136] Stereochemistry of **266** was assigned on the basis of attack of the Grignard from the more accessible *exo* face of the carbonyl functionality in **243** (Scheme 107). Alcohol **266** was obtained as a pale yellow oil following purification of the crude reaction by column chromatography (6:1 hexane/ethyl acetate).



243 **266**

Scheme 107

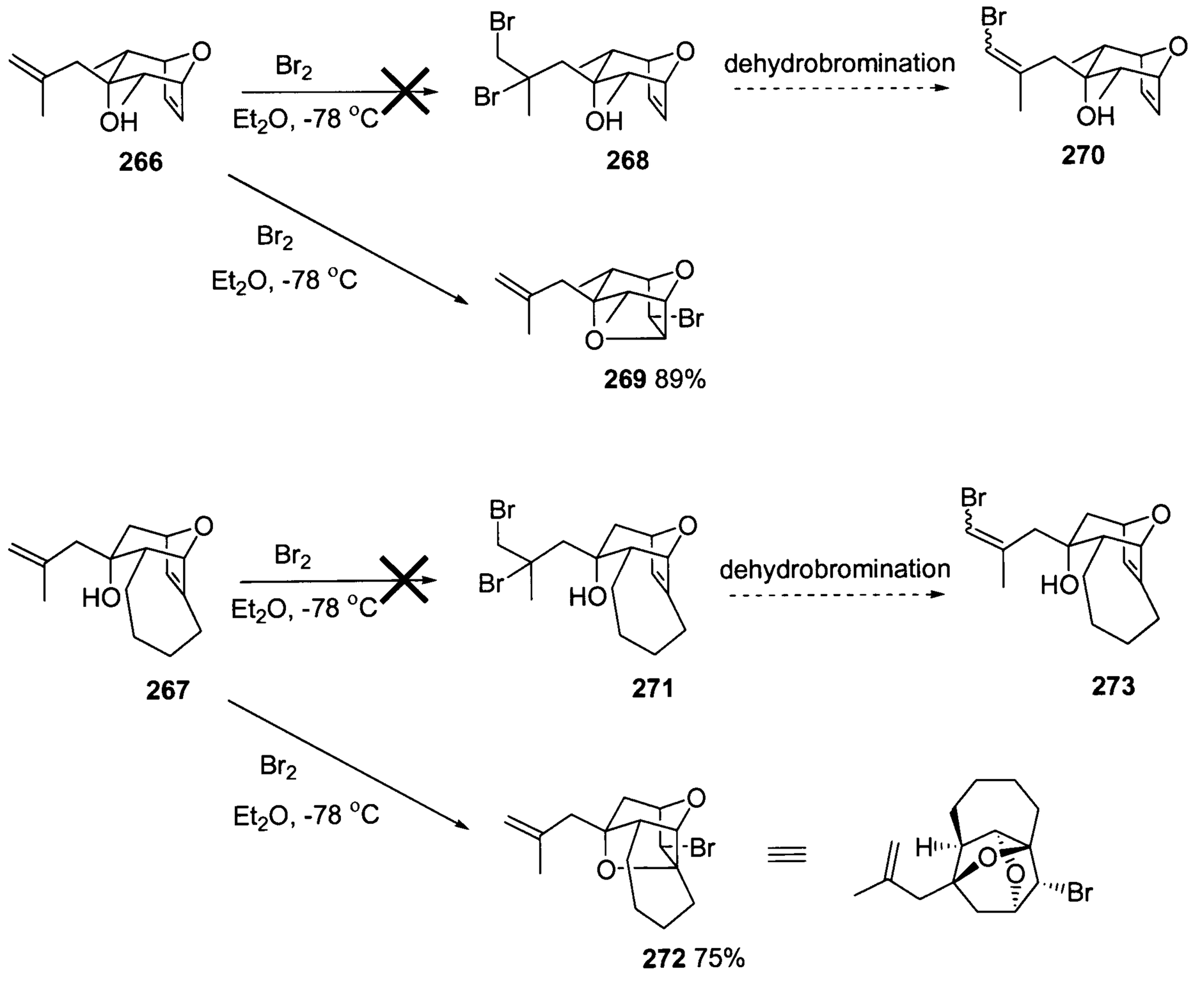
Tricyclic ketone **195** was then tested with 2-methylallylmagnesium chloride under same conditions as model ketone **243**. Pleasingly, nucleophilic addition to tricyclic ketone **195** using 2-methylallylmagnesium chloride in diethyl ether at -78 °C afforded desired alcohol **267** in excellent yield. The crude reaction was purified by column chromatography (3:1 hexane/ethyl acetate) to yield compound **267** as the only product in 87% yield (Scheme 108).[132] The stereochemistry of the alcohol in **267** was assumed to be *endo* since the reaction gave only one product and attack from the *exo* face of the carbonyl motif would be much preferred on steric grounds.



195 **267**

Scheme 108

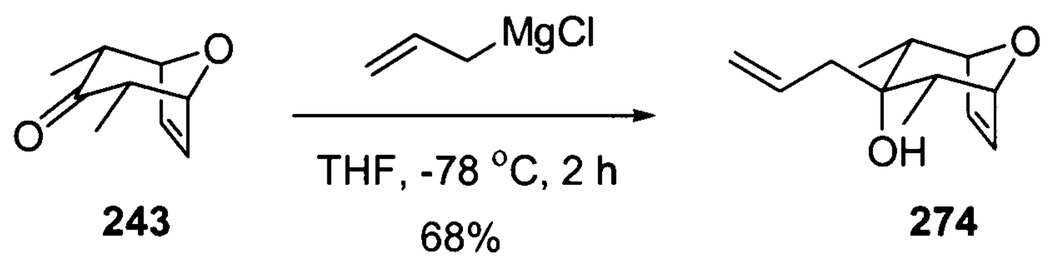
Attempted selective bromination of alkenes **266** and **267** was thwarted by the higher reactivity of the internal alkene to provide bromoethers **269** and **272** in 89 and 75% yield respectively (Scheme 109).[135] Formation of bromo ethers **269** and **272** illustrates the close proximity of the axial-orientated alcohol to the internal double bond. The results confirm the *exo* face of attack by the nucleophile in Schemes 107 and 108. Formation of **269** and **272** can be attributed to attack of the bromine from the less hindered *exo*-face of the internal alkene, followed by intramolecular capture of the bromonium ion intermediate by the axial alcohol. Interestingly bromoether **272** contains the *trans* arrangement in the [4.4.1] carbocyclic system (Scheme 109).



Scheme 109

Following the successful addition of 2-methylallylmagnesium chloride to ketone **243**, addition of allyl Grignard to compound **243** was also investigated (Scheme 110). It was hoped that allylation of **243** would lead to alcohol **274** that could subsequently be converted into β-hydroxy ketone **258** through a Wacker oxidation following protection of the axial alcohol.

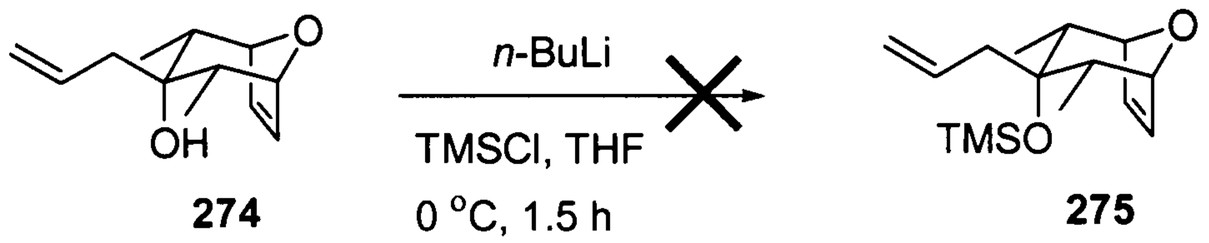
In the event, addition of allylmagnesium chloride to **243** in tetrahydrofuran at -78 °C for 2 h provided a single diastereomer assumed to be compound **274**. The crude reaction was purified by column chromatography (6:1 hexane/ethyl acetate) to afford **274** in 78% yield (Scheme 110).[137]



Scheme 110

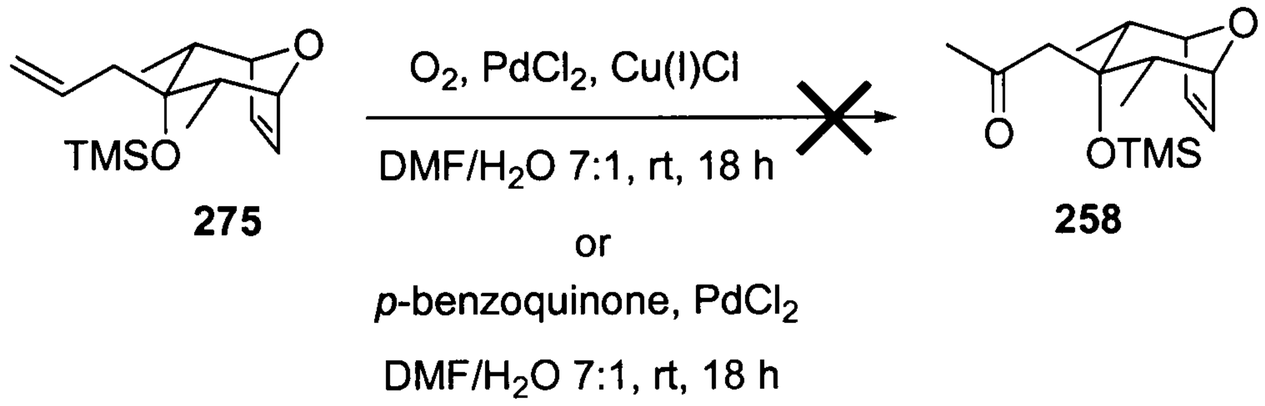
Attempted protection of alcohol **274** using trimethylsilyl chloride in the presence *n*-butyllithium in tetrahydrofuran at 0 °C only resulted in the recovery of starting material (Scheme 111). This outcome further highlights the hindered nature of the axial oriented alcohol in compound **274**.[81]

Fortunately, the situation was rescued when **274** was reacted with trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C. This variant provided a preparatively useful yield of protected alcohol **275** (Scheme 111).



Scheme 111

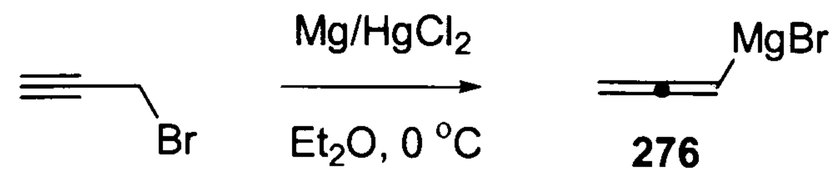
Attempted Wacker oxidation of **275** using palladium (II) chloride, copper (I) chloride and oxygen or palladium (II) chloride in the presence of *p*-benzoquinone were frustrated by the recovery of starting material (Scheme 112).[138]



Scheme 112

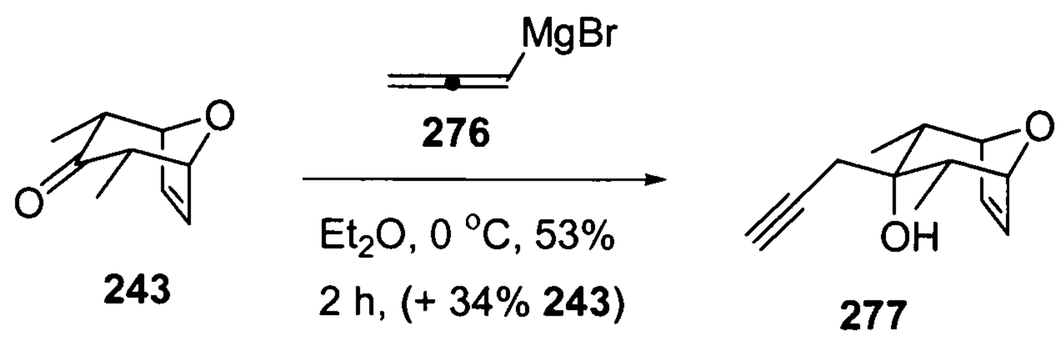
Given the unexpected outcome of Scheme 112, the choice of Grignard was changed from allyl to allenyl Grignard in the hope that the ensuing propargylic product could be converted into compound **258** following hydration of the terminal alkyne.

Towards this end, allenylmagnesium bromide **276** was readily prepared from propargyl bromide and magnesium in the presence of mecury (II) chloride in diethyl ether at 0 °C (Scheme 113).[139]



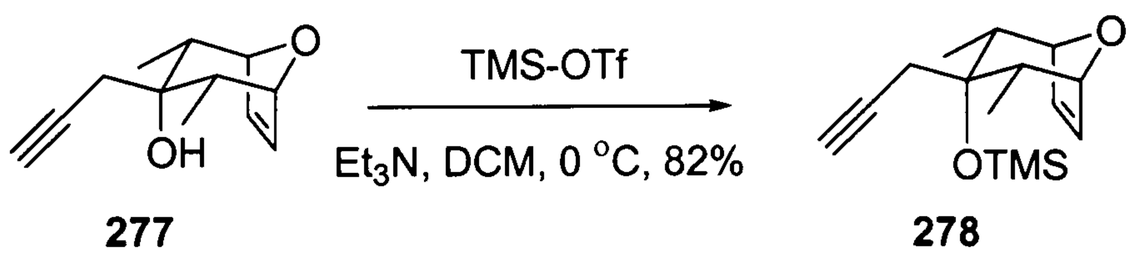
Scheme 113

The reaction between ketone **243** and freshly prepared allenylmagnesium bromide **276** proceeded without incident in diethyl ether at 0 °C (Scheme 110). The crude reaction was purified by column chromatography (3:1 hexane/ethyl acetate) to give first recovered ketone **243** in 34% yield, followed by a homo propargylic product assumed to be **277** in 53% yield (Scheme 114).[140]



Scheme 114

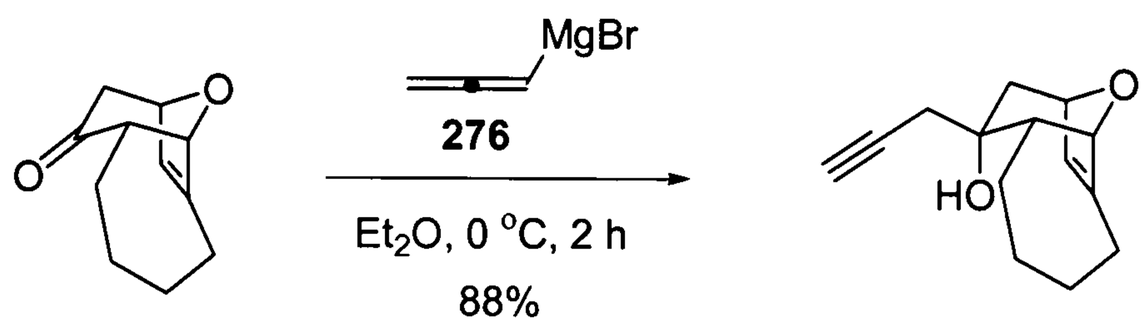
Protection of alcohol **277** was effected using trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C. Under these conditions trimethylsilyl ether **278** was obtained as a pale yellow oil in excellent yield (scheme 115).



Scheme 115

Direct addition of allenylmagnesium bromide **276** to tricyclic ketone **195** proceeded readily in diethyl ether at 0 °C (Scheme 116). Under these reaction conditions alkyne

279 was obtained as a colourless oil in 88% yield following purification of the crude reaction by column chromatography (3:1 hexane/ethylacetate).[140]

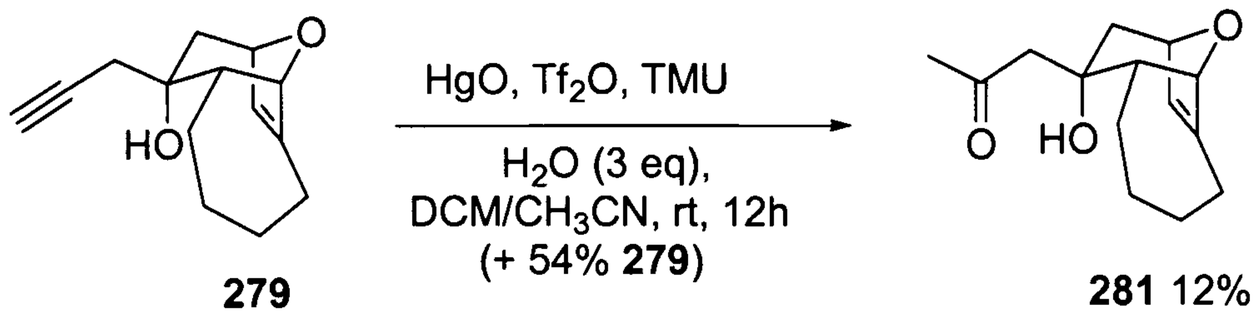


195 **279**

Scheme 116

Nishizawa has reported the use of mercuric triflate-*N*,*N*,*N*',*N*'-tetramethylurea complex as a highly effective catalyst for the hydration of terminal alkynes to methyl ketones under mild conditions.[141]

Towards this end, attempted hydration of alkyne **279** using mercury (II) oxide, trifluoromethanesulfonic anhydride and *N*,*N*,*N*',*N*'-tetramethylurea in acetonitrile and dichloromethane in the presence of three equivalent of water at room temperature for 12 h provided only 12% of the required *β*- hydroxyketone **281** along with 54% recovered starting material. In addition diether **280** resulting from reaction at the internal double bond of **279** was also isolated in 3% yield (scheme 117). Formation of **280** is further evidence that allenylation of ketone **195** must have occurred from the less sterically hindered *exo* face of the carbonyl group in **195**.

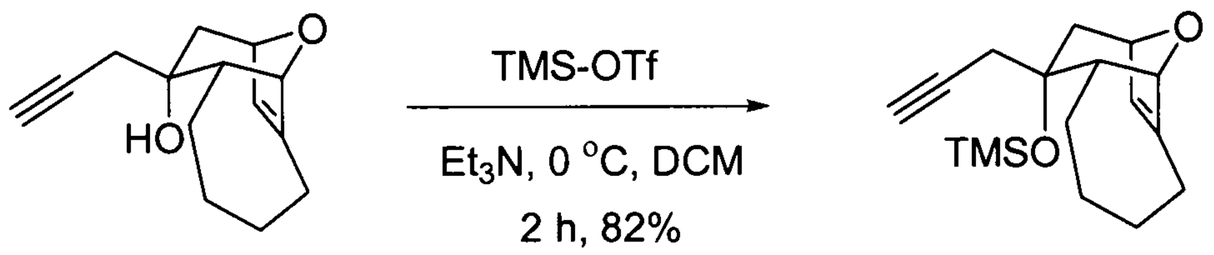


279 **281** 12%

280 3%

Scheme 117

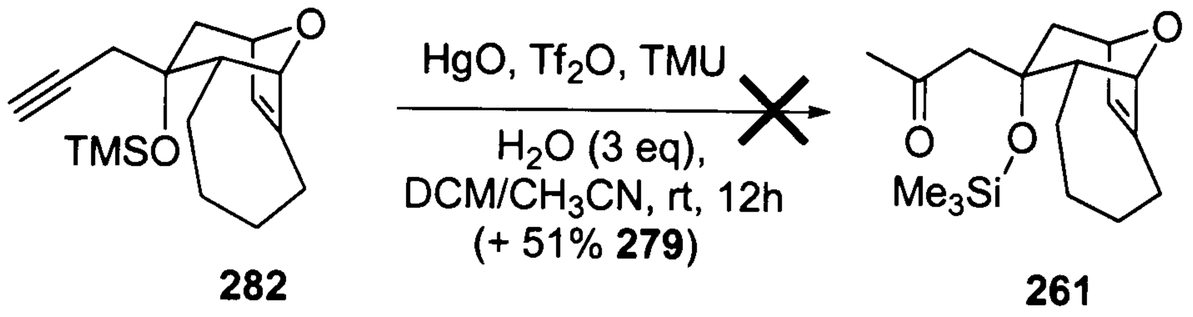
The protection of compound **279** was accomplished using trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C. Under these reaction conditions silylated product **282** was obtained as an oil in excellent yield (Scheme 118).



279 **282**

Scheme 118

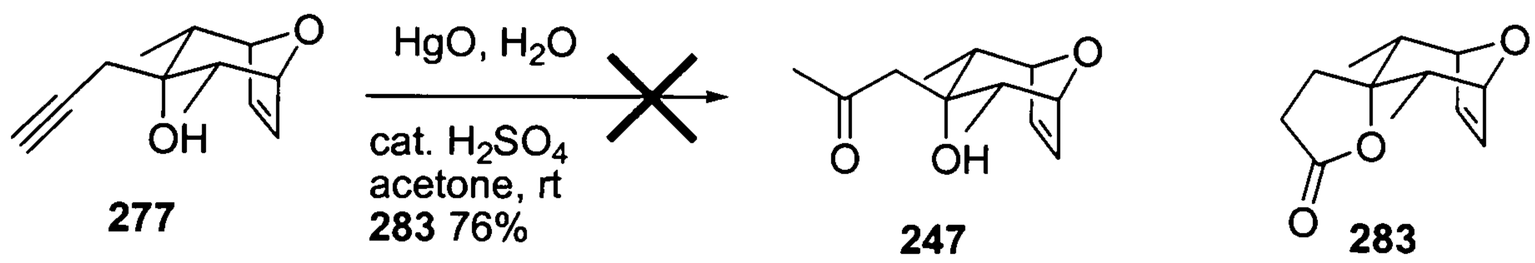
Attempted hydration of alkyne **282** under Nishizawa's protocol gave desilylated starting material **279**. Formation of the desired silylated ketone **261** was not observed, instead silyl deprotected ketone **281** was isolated in 7% yield (Scheme 119).[141] Although compound **281** could potentially be converted into **261**, the low yield of **281** in the reaction made this synthetic route to **261** unattractive (Scheme 119).



Scheme 119

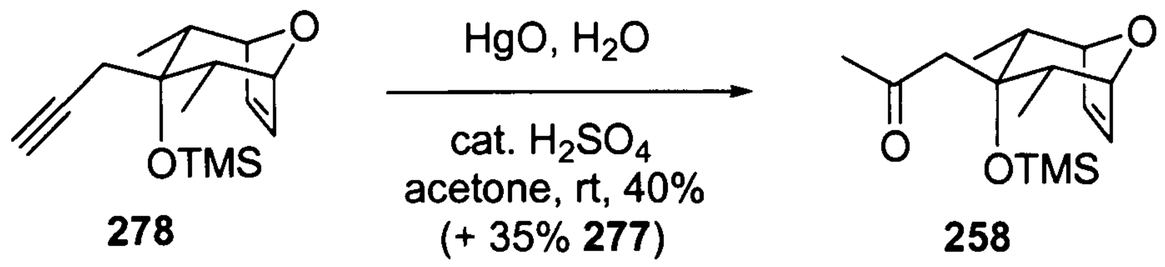
Attempts to find better hydrolysis conditions led to the use of mercury (II) oxide in the presence of catalytic amounts of sulphuric acid in wet acetone.

In the event, attempted hydrolysis of alkyne **277** using mercury (II) oxide in the presence of catalytic amounts of sulphuric acid in a mixture of water and acetone at room temperature gave none of the desired β-hydroxyketone **247**. Instead, formation of lactone **283** was observed in 76% yield (Scheme 120).[142]



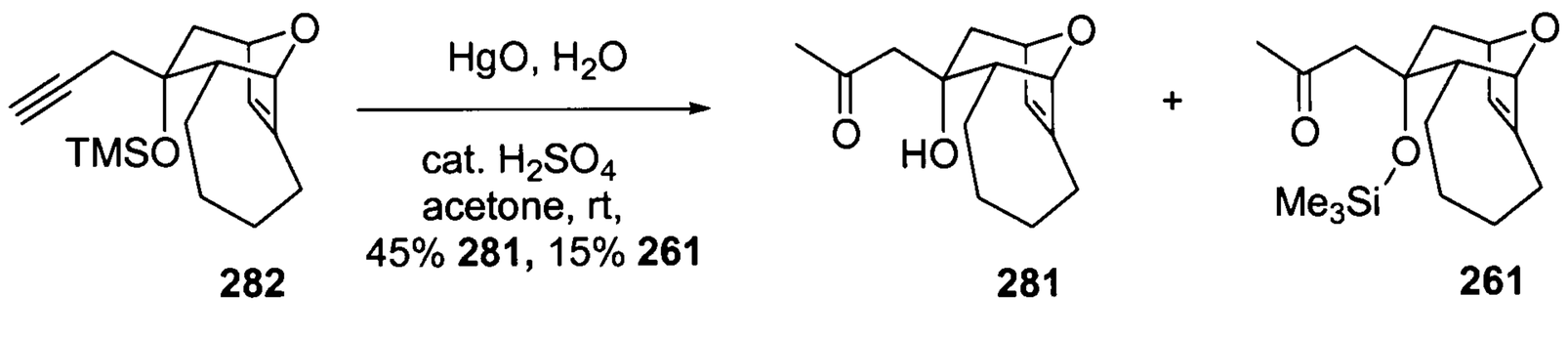
Scheme 120

Hydrolysis of silylated alkyne **278** was accomplished using mercury (II) oxide in wet acetone in the presence of catalytic amounts of sulphuric acid. Although the reaction was accompanied by significant amounts of silyl deprotection, the desired protected ketone **258** could be isolated in a useful 40% yield (Scheme 121).[142]



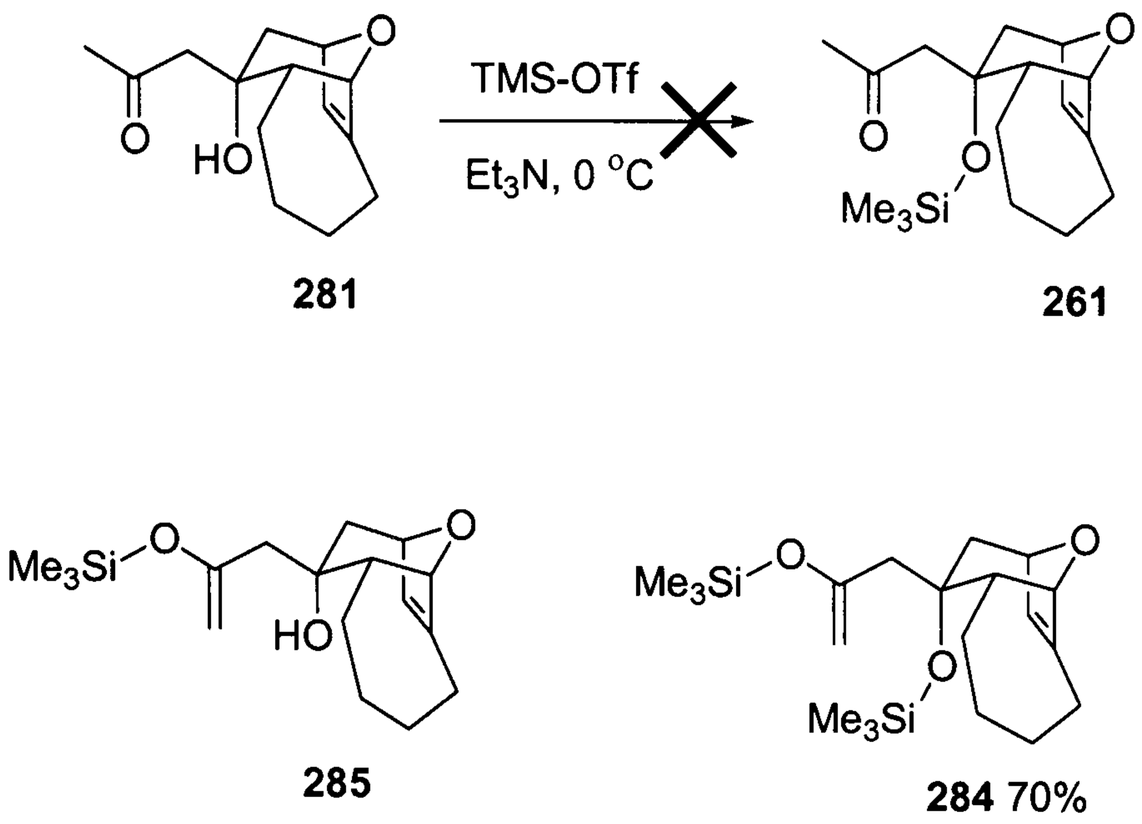
Scheme 121

Hydrolysis of the terminal alkyne of **282** was accomplished under the same conditions as model compound **278** using mercury (II) oxide in wet acetone in the presence of catalytic amounts of sulphuric acid (Scheme 121). Under these conditions the desired product **261** was obtained in 15% yield, accompanied by silyl deprotection product **281** in 45% yield (Scheme 122).[142]



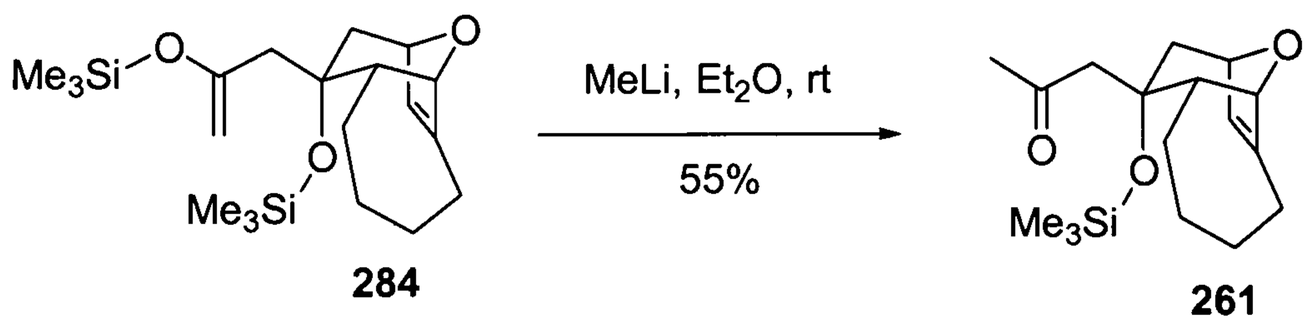
Scheme 122

Attempted reprotection of β-hydroxyketone **281** using 2.5 equivalents of trimethylsilyl triflate in the presence of triethylamine in dichloromethane at 0 °C gave none of the required silylated ketone **261**. The reaction gave the doubly silylated product **284** in 70% yield. Efforts to limit the formation of **284** by using one equivalent of trimethylsilyl triflate indicated (by TLC) formation of silylenol ether **285**, again pointing to the hindered nature of the axial alcohol in compound **281** (Scheme 123).



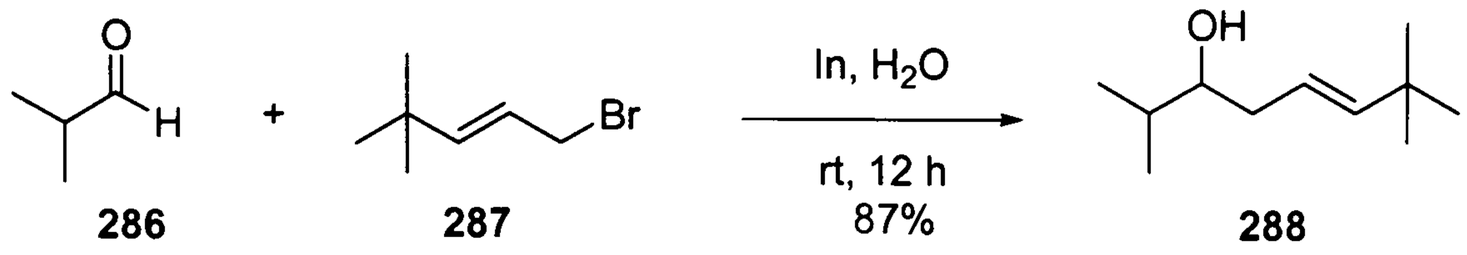
Scheme 123

Bis-silylated compound **284** was converted to required silyl ether **261** using two equivalents of methyllithium in diethyl ether at room temperature to generate the corresponding enolate and then quenching with water. Under these conditions compound **261** was isolated as a colourless oil in 55% yield following purification of the crude reaction mixture by column chromatograpghy (4:1 hexane/ethyl acetate) (Scheme 124).[143]



Scheme 124

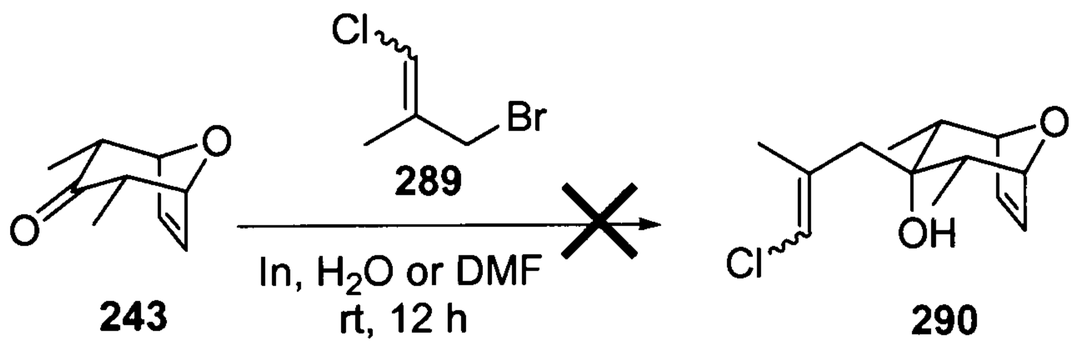
Loh reported a highly α-regioselective indium mediated allylation of carbonyl compounds in water. For example the reaction of isopropyl aldehyde **286** with bromide **287** in the presence of indium in water at room temperature for 12 h and then heating at 40 °C for another 12 h gave α-adduct **288** in 87% yield (Scheme 125).[144a]

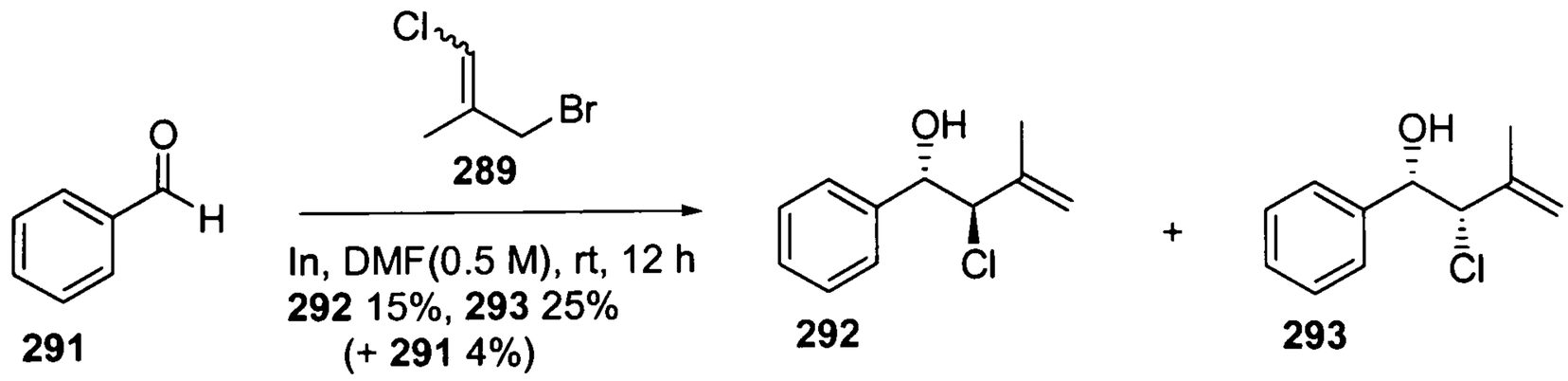


Scheme 125

It was anticipated that a one pot allylation reaction between ketone **243** and a suitable allyl halide using Loh's methodology could deliver the required vinyl halide **290**. This particular strategy to compound **290** was attractive in that, the reaction could take place in water thereby alleviating the need to handle flammable and anhydrous organic solvents.

In the event attempted direct formation of vinyl chloride **290** by indium-mediated allylation reaction between ketone **243** and allylbromide **289** in either water or *N*,*N*-dimethylformamide at room temperature only gave recovered starting material (Scheme 126).



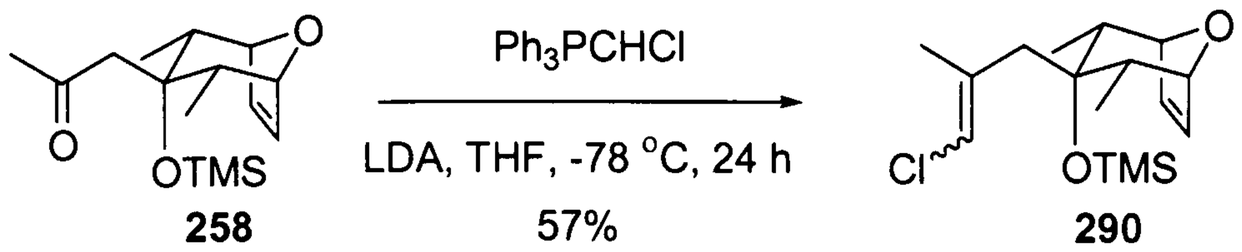


Scheme 126

In order to verify if the expected organoindium species was formed in the reaction, allylation of benzaldehyde **291** using allylbromide **289** under the same conditions as ketone **243** was tried. In the event, the reaction provided recovered starting material in 4% yield, followed by a separable mixture of homoallylic alcohols **292** and **293** in a ratio of 1:2 in 40% overall yield (Scheme 126). It is known that indium mediated allylation using high concentrations (10 M) of water as solvent give exclusively the α-adduct while reactions using other solvents such as *N*,*N*-dimethylformamide at lower concentrations give exclusively the γ-adduct.[145] In this regard, formation of γ-adducts **292** and **293** under the reaction conditions is consistent with the literature. Furthermore, reaction of allylindium reagents bearing chlorine or bromide at the γ-position, are known to give high *cis*-selectivity.[145] Hence, formation of *cis*-homoallylic alcohol **293** as the major product in the reaction is also consistent with the literature even though the *trans*/*cis* ratio was lower than expected (Scheme 126).

Although the attempted indium-mediated allylation of ketone **243** did not provide any of alkylidenecarbene precursor **290** the reaction of Schemes 102 and 121 had provided adequate amounts of protected β-hydroxy ketone **258** that could be converted into compound **290**.

It was anticipated that ketone **258** could be converted into vinyl chloride **290** through a Wittig reaction. In the event, a Wittig reaction between ketone **258** and the *in situ* generated ylide of (chloromethyl)triphenylphosphine in tetrahydrofuran at -78 °C afforded a separable 1:1 mixture of geometrical chloroalkenes **290** in 57% overall yield (scheme 127).[116]

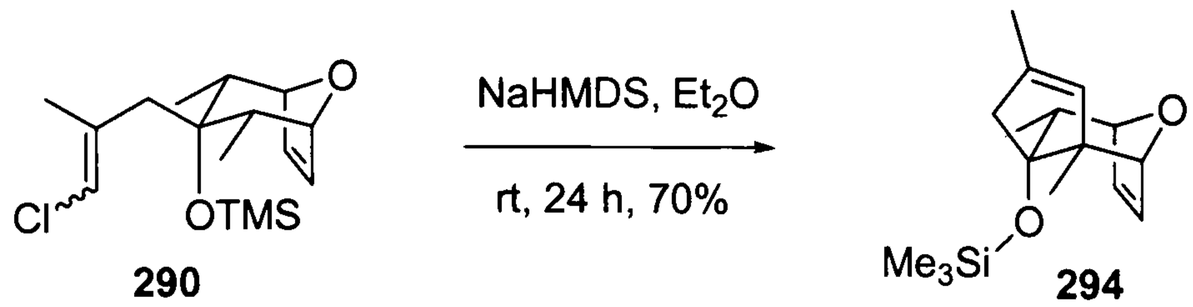


Scheme 127

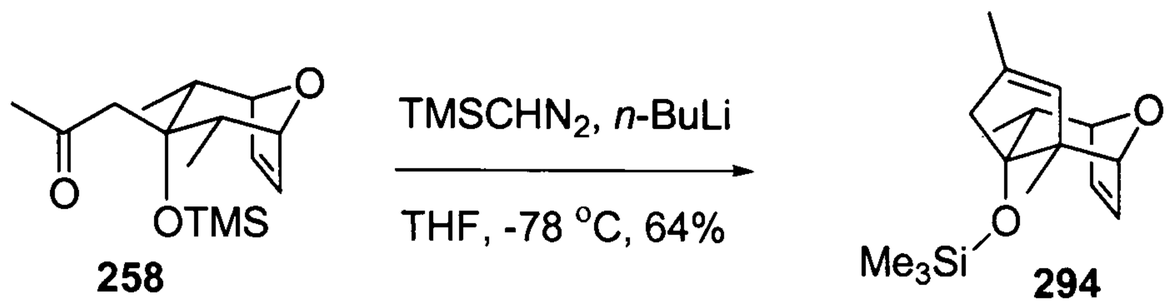
3.2.2 Synthesis of tricyclic ether 294

Attempted intramolecular alkylidenecarbene 1,5 C-H insertion reaction of a mixture of geometrical chloroalkenes **290** was effected by treatment with 3.5 equivalent of sodium bis(trimethylsilyl)amide in diethyl ether at room temperature for 24 h. Under these conditions cyclopentene **294** was isolated as a colourless oil in 70% yield (Scheme 128). Although the stereochemistry of the chloroalkenes was irrelevant as both isomers gave rise to the same product, it was interesting to observe by thin layer chromatography that (*E*)-**290** underwent 1,5 C-H insertion faster than (*Z*)-**290** under identical reaction conditions (Scheme 128).

Alkene **294** was also prepared when silylated ketone **258** reacted with 1.5 equivalent of in situ generated lithiotrimethylsilyldiazomethane in tetrahydrofuran at -78 °C. Purification of the crude reaction mixture by column chromatography (3:1 hexane/ethyl acetate) provided cyclopentene **294** in 64% yield (Scheme 128).[146]



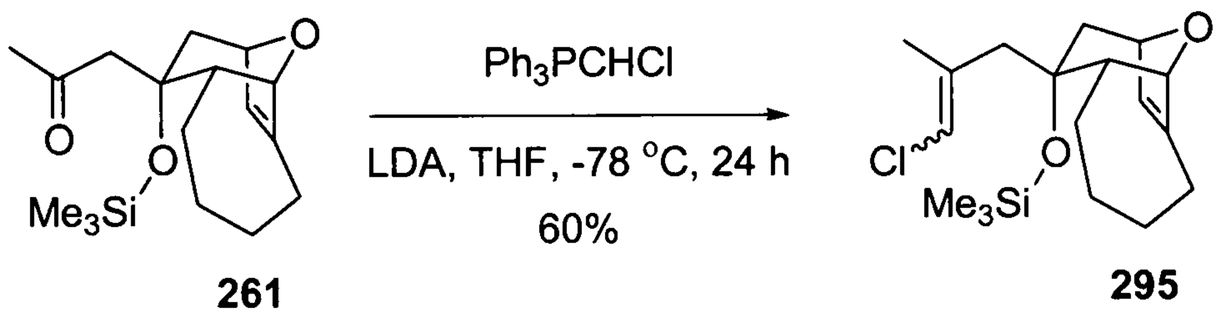
290 **294**



258 **294**

Scheme 128

Attempted Wittig reaction between protected β-hydroxyketone **261** and the ylide of (chloromethyl)triphenylphosphine proceeded uneventfully in tetrahydrofuran at -78 °C to give a 1:1 mixture of geometrical chloroalkenes **295** as a pale yellow oil in 60% overall yield (Scheme 129).



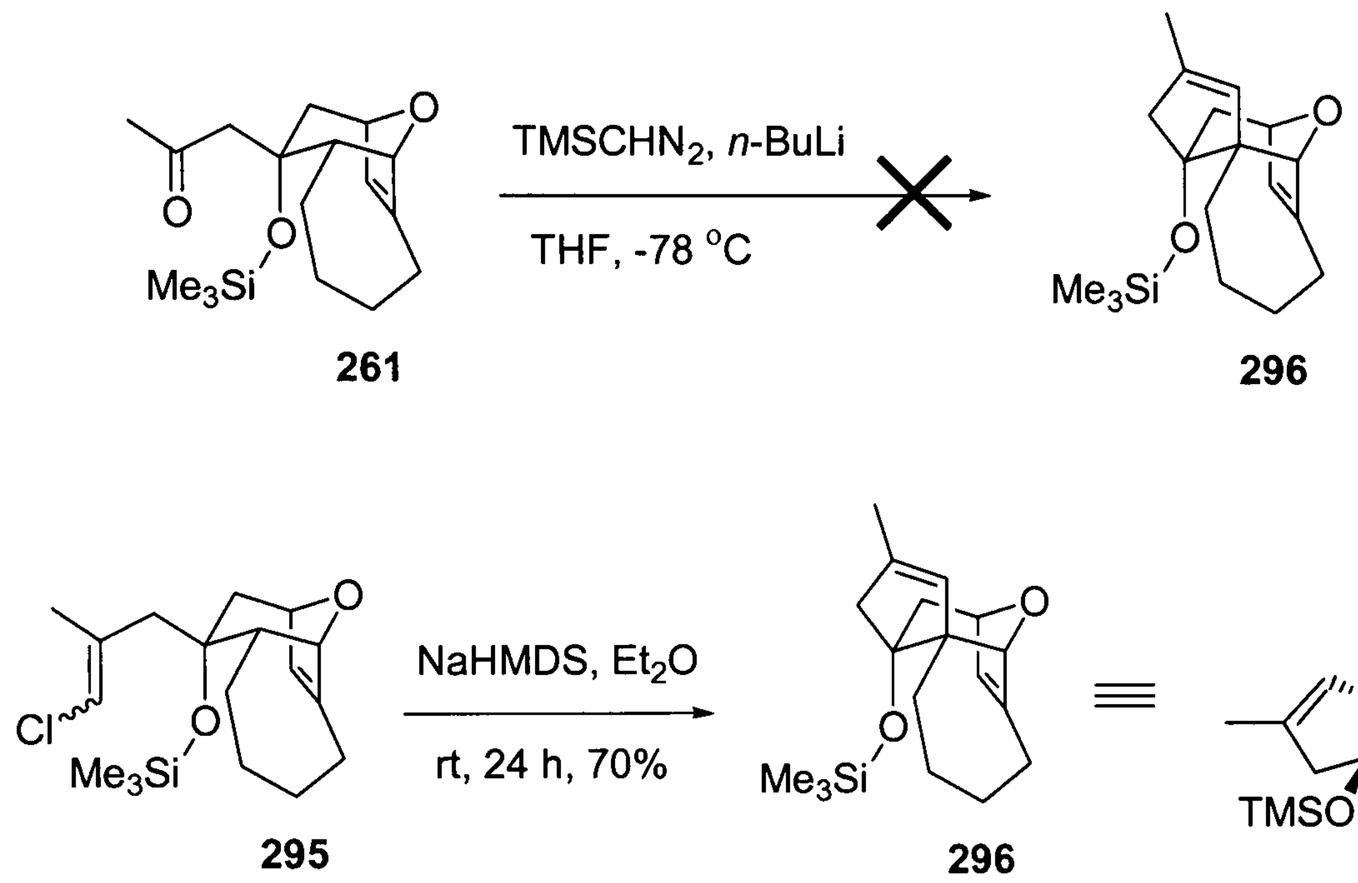
261 **295**

Scheme 129

3.2.3 Synthesis of tricyclic ether 296

Attempted selective 1,5 C-H alkylidenecarbene reaction of silylated ketone **261** using the anion of (trimethylsilyl)diazomethane in tetrahydrofuran at -78 °C was frustrated by the recovery of starting material (Scheme 130). The lack of reaction of **261** gave a real cause for concern as under same reaction conditions the structurally similar compound **258** (Scheme 128) had reacted.

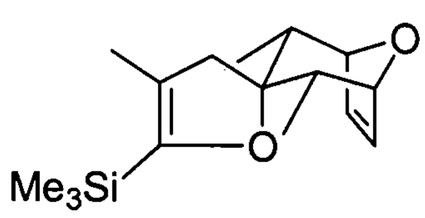
Fortunately, when a mixture of geometrical chloroalkenes **295** was treated with sodium bis(trimethylsilyl)amide at room temperature for 24 h in diethyl ether, compound **295** underwent selective alkylidenecarbene 1,5 C-H to give the desired cyclopentene **296** in excellent yield (Scheme 130). Tricyclic adduct **296** was obtained as a colourless oil following purification of the crude reaction mixture by column chromatography (5:95 ethyl acetate/hexane).



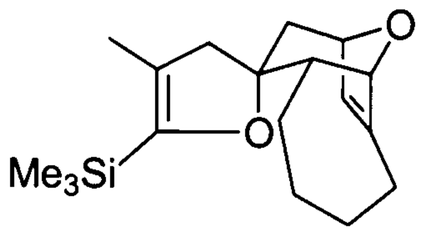
Scheme 130

3.2.4 Why is 1,5 C-H bond insertion preferred over 1,5 O-Si bond insertion?

Although alkylidenecarbenes are known to undergo intramolecular 1,5 O-Si insertion reactions to substituted dihydrofuran derivatives, and this has been shown to proceed more rapidly than 1,5 C-H insertion in the case of **258**, **290** (Scheme 128) and **295** (Scheme 130), formation of **297** and **298** (Figure 6) arising from 1,5 O-Si insertion reaction were not observed.



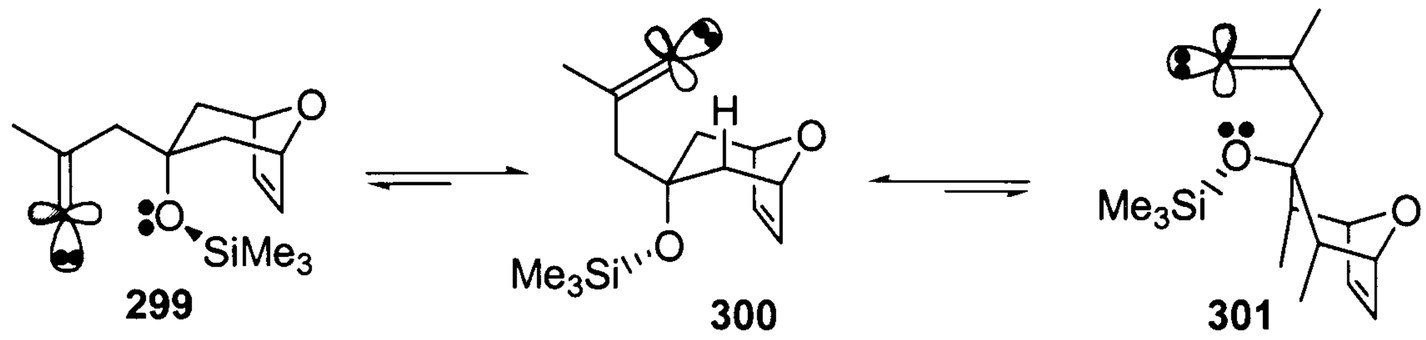
297



298

Figure 6

There are two plausible reaction pathways for the 1,5 O-Si insertion, a concerted O-Si insertion, or a reaction pathway involving interaction of the vacant p-orbital of the carbenic carbon with an oxygen lone pair to yield a transient oxonium ylide that undergoes a 1,2 silyl migration (Scheme 78). The absence of **297** and **298** suggest that the conformations **299** or **301** which would allow maximum orbital interactions leading to their formation are not favoured (Scheme 131). In the lowest energy conformation **300**, the bulky trimethylsilyl group is *exo* to the oxabicyclic ring system thereby placing the lone pairs on the oxygen in an *endo* position thereby eliminating the possibility of any interactions with the carbenic carbon and hence allowing 1,5 C-H insertion pathway to dominate (Scheme 131).



Scheme 131

In order to gain further information, molecular mechanics calculations were carried out on the simplified model **302** (Figure 7) using the Sybyl force field in Spartan IBM version 5.1.3 X11 (wavefunction, Inc).[147] Geometry optimization for both chair **302** and boat **303** conformations indicated that the lowest boat conformation was 7.9 kcal/mol higher in energy than the chair. The trimethylsilyl group in both cases was orientated gauche to the methyl group around the carbon-oxygen bond (CH_3-C-O-Si dihedral angle 51.1° for chair **304** and 52.2° for boat **305**, Figure 7).

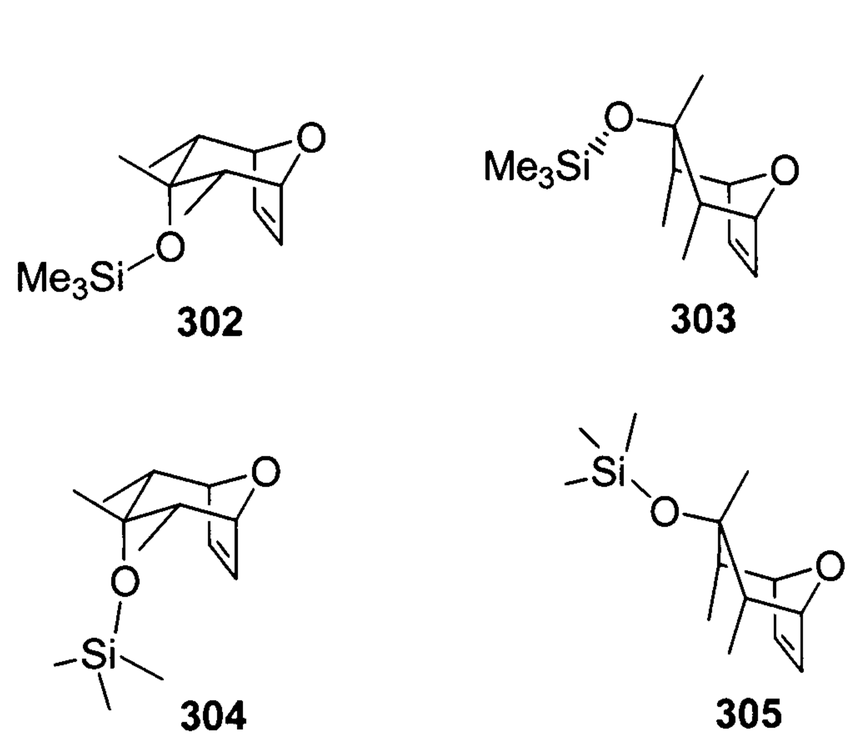


Figure 7

Rotation about this carbon-oxygen bond in the chair form showed a conformation where the lone pair and methyl group are synperiplanar to be 6.1-6.5 kcal/mol higher in energy than the lowest energy gauche conformation. Similarly, in the boat form, the synperiplanar orientation of methyl and the oxygen lone pair is 5.5 kcal/mol higher in

energy than the gauche conformation. These calculated results for simplified model **302** suggests that a conformation in which the oxygen lone pair is able to interact with the empty p-orbital of the carbenic carbon is energetically unfavourable, hence offering a possible explanation as to why formation of **297** and **298** is not be observed.

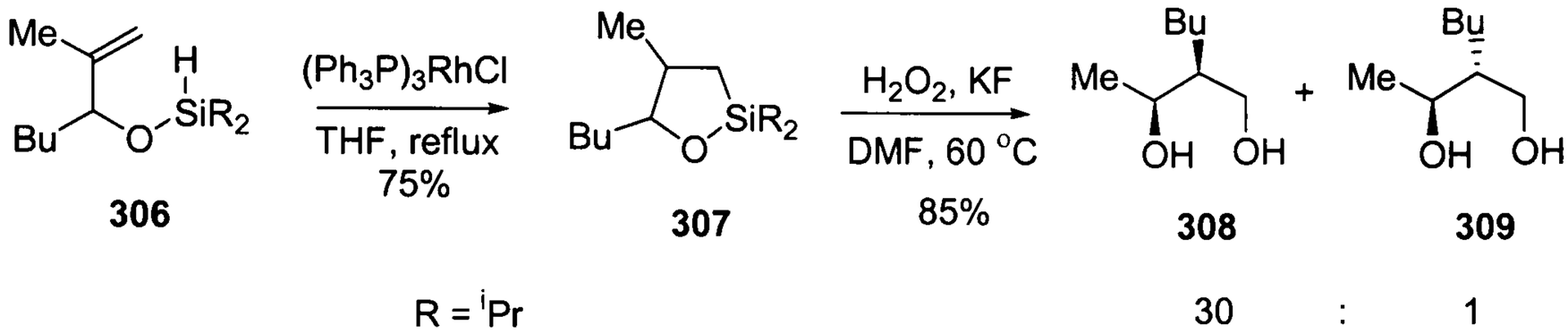
3.3.0 Conclusion

In conclusion, two successful methods based on dianion and allenyl Grignard addition to [3.2.1] oxabicyclic ketones have been developed as a synthetic alternative to the aldol reaction with acetone. Protected β-hydroxy ketones are converted by a Wittig reaction into vinyl chlorides as alkylidenecarbene precursors. A rare intramolecular selective 1,5 C-H bond insertion over 1,5 O-Si bond insertion has been used to construct the A-ring system of ingenol thereby assembling the core ABC skeleton of the natural product with the correct functionalities at C-2 and C-4 in addition to a bridgehead double bond that may be converted into the *trans* ring junction.

CHAPTER 4

4.1.0 Introduction

Intramolecular hydrosilylation of olefins is a process which results in the addition of a silicon-hydrogen bond across a double bond giving rise to cyclic siloxane intermediate **307** (Scheme 132). Such reaction is often catalysed by a transition metal usually platinum or rhodium.[148]



Scheme 132

The silicon-carbon bond of the oxasilacyclic intermediate **307** can be oxidatively cleaved to give synthetically useful polyoxygenated skeletons **308** and **309** with retention of configuration. The overall stereochemical outcome of the reaction may be explained with reference to conformations **310** and **311** of the presumed intermediates (Figure 8).

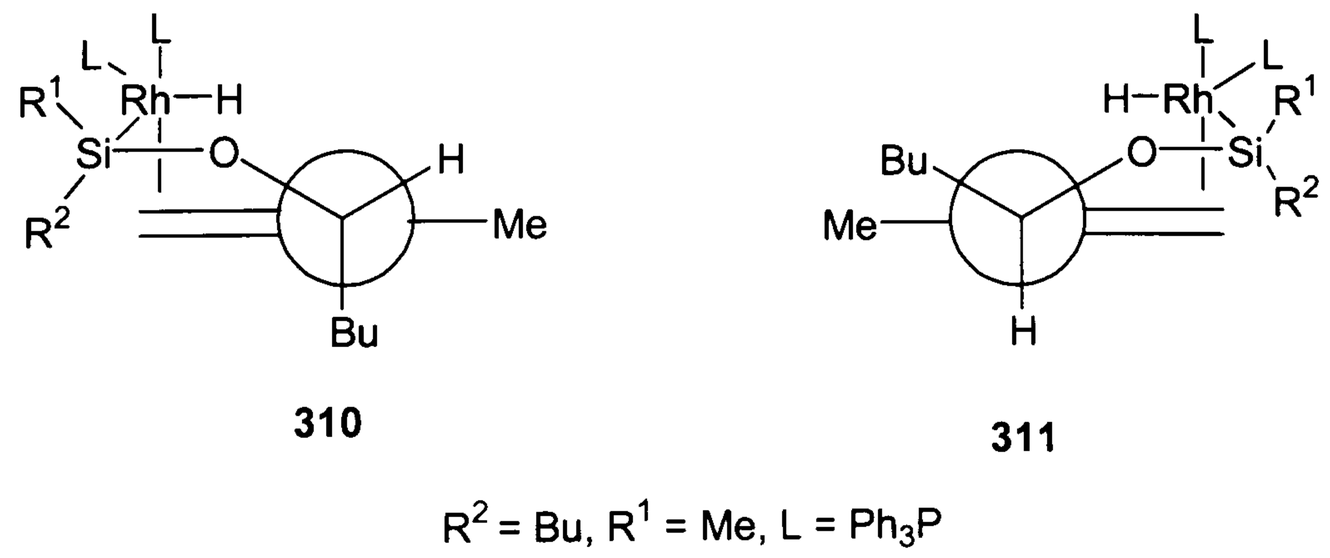
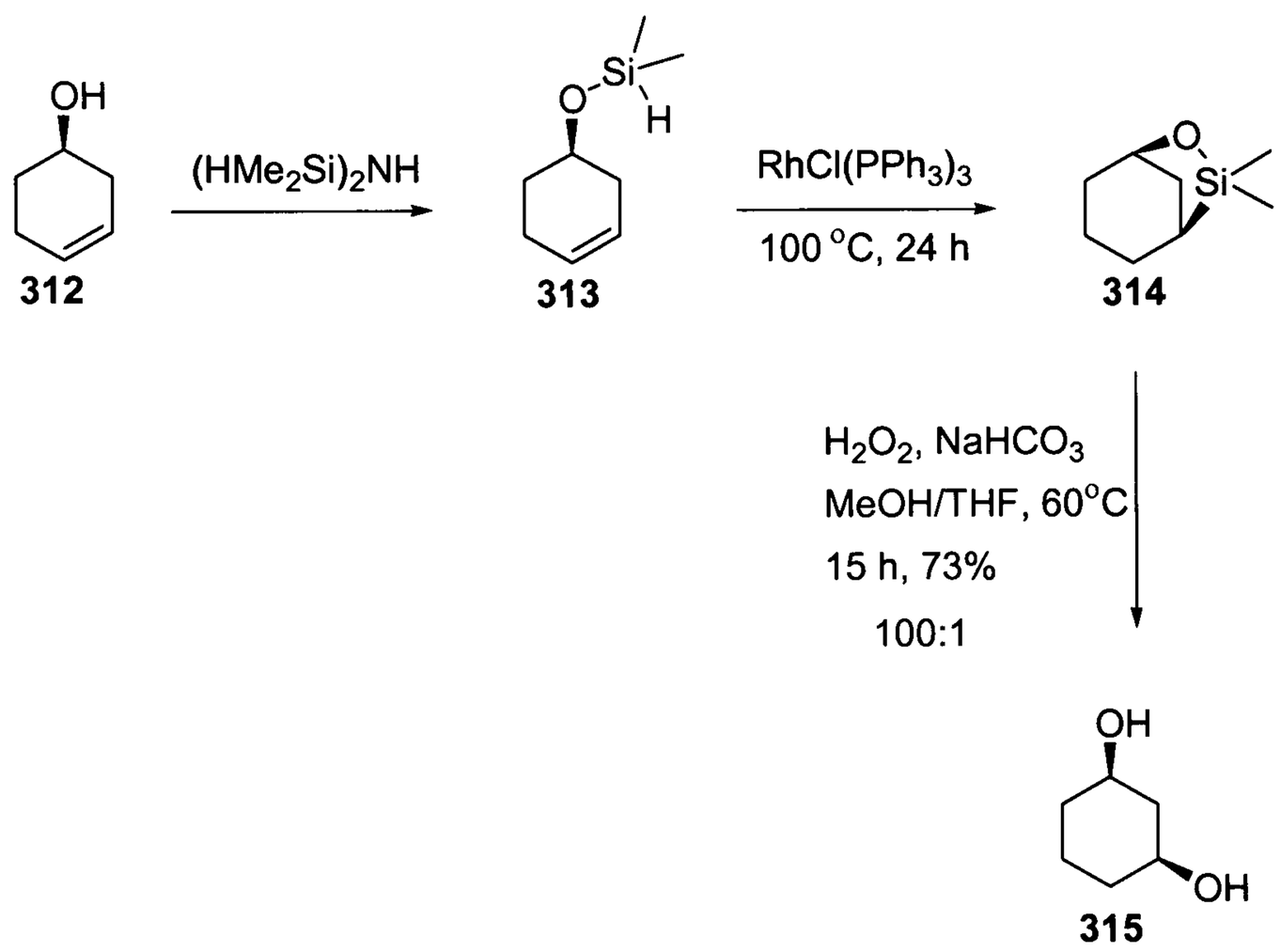


Figure 8

The major product **308** is thought to have arisen from conformation **310** as it allows the bulky butyl substituent to occupy an *anti* position which is preferred sterically. Conformation **311** is less favourable owing to steric interactions between the butyl and the methyl groups and leads to the minor isomer **309** (Figure 7).[149]

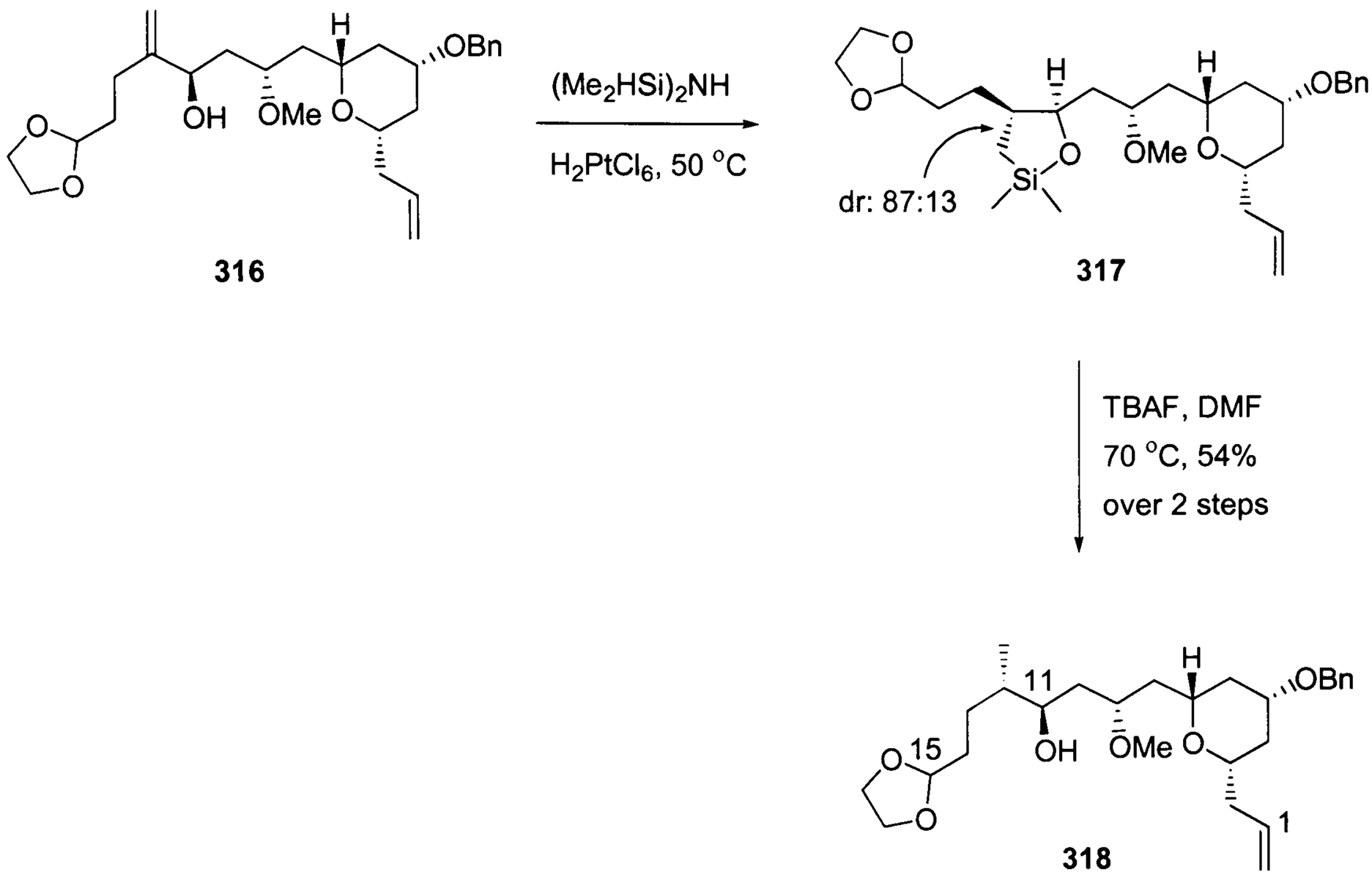
Tamao reported that the hydroxyl group of homoallylic alcohol **312** can be used to direct a hydrosilylation reaction resulting in the formation of **314**, the silicon–carbon bond of which was oxidized to diol **315** with retention of stereochemistry (Scheme 133).



Scheme 133

This synthetic strategy was recently utilised by Kozmin in the construction of the C1-C15 fragment of the marine macrolide leucascandrolide A (Scheme 134). Conversion of alcohol **316** into the corresponding silyl ether using tetramethyldisilazane followed by treatment with cloroplatinic acid in benzene at 50 °C resulted in diastereoselective formation of silacycle **317** (dr 85:15). Protodesilylation of **317** using

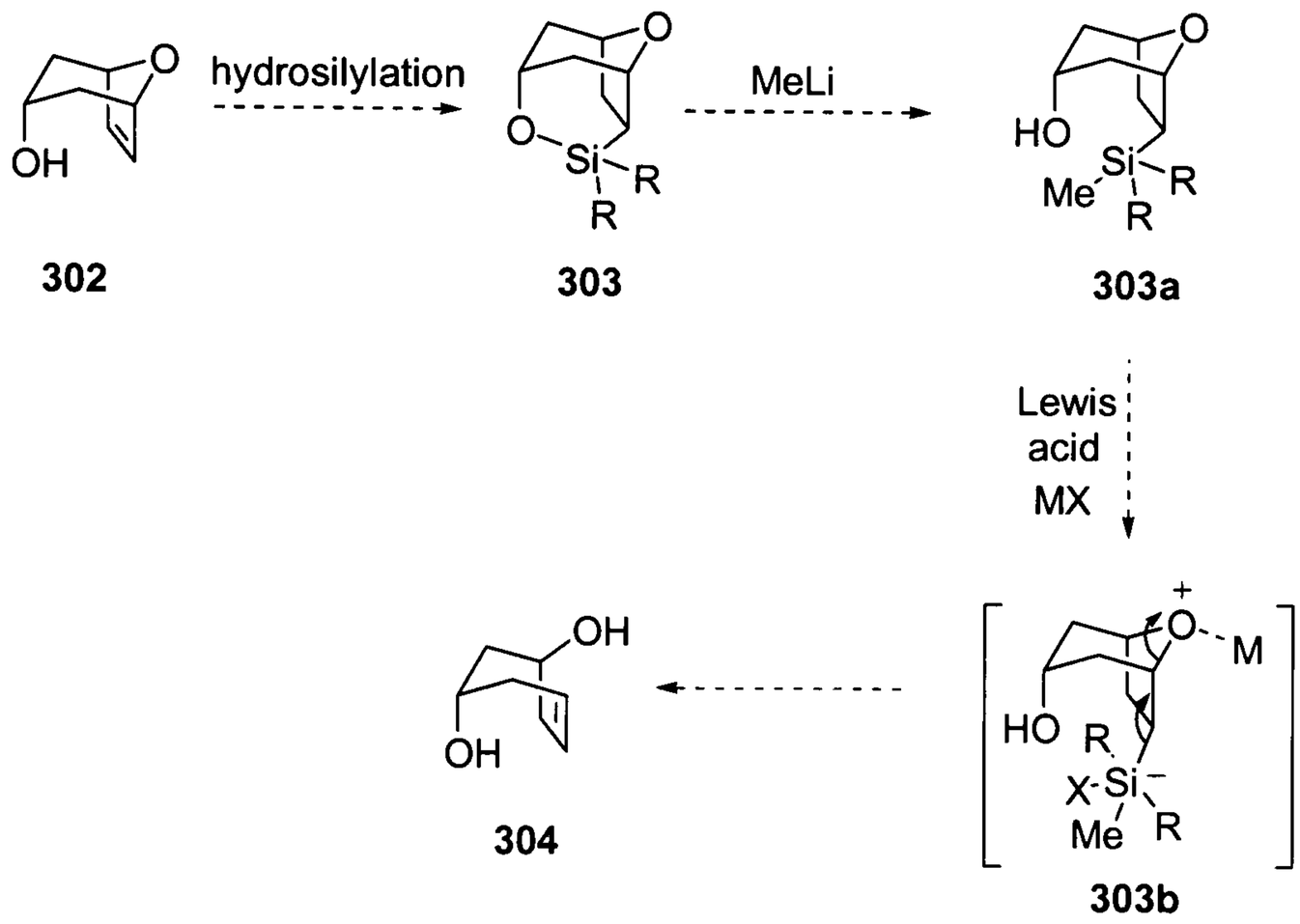
tetrabutylammonium fluoride gave fragment **318** of leucascandrolide A (Scheme 134).[150]



Scheme 134

4.2.0 Results and Discussion III

It was anticipated that substrate directed hydrosilylation of known alcohol **302** would render silacycle **303**. Addition of a suitable nucleophile to compound **303** could lead to silyl ether **303a**. Alcohol **303a** in the presence of a Lewis acid may produce the ionic intermediate **303b** that could undergo a Peterson-like *anti*-elimination to diol **304** (Scheme 135).[151]

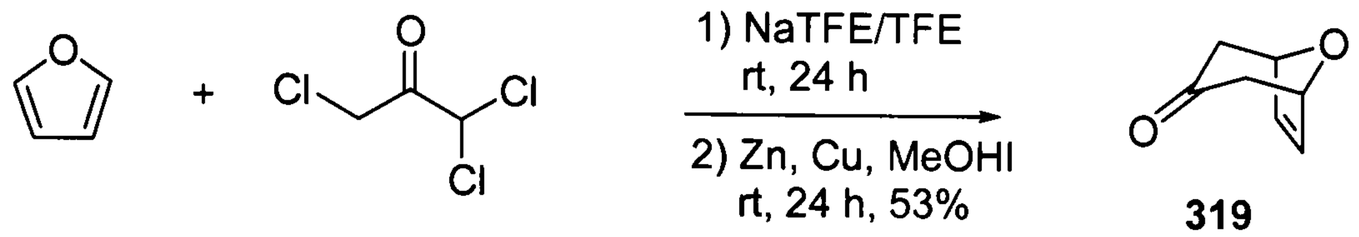


Scheme 135

Towards this end the precursor to alcohol **302**, the [3.2.1]oxabicyclic ketone **319**, was synthesized (Scheme 136).

An intermolecular reaction between furan and 1,3,3-trichloropropan-2-one was effected using $NaOCH_2CF_3$ (NaTFE) as base in trifluroethanol at room temperature for 24 h. Under these conditions, a dark yellow residue was obtained that was taken up in methanol and added to a zinc-copper mixture in methanol at room temperature and stirred for 24 h. The crude reaction mixture was purified by column chromatography

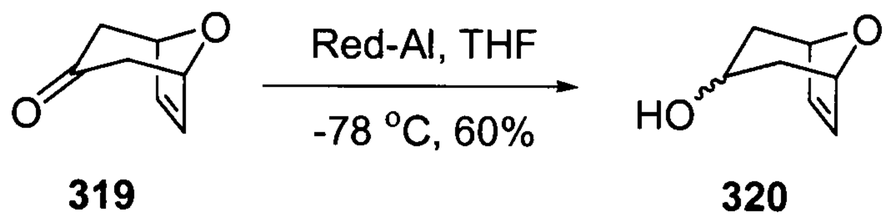
(4:1 60-80 petroleum ether/ethyl acetate) to give desired ketone **319** in 53% yield over two steps (Scheme 136).



319

Scheme 136

Attempted selective reduction of ketone **319** using sodium bis-(2-methoxyethoxy)aluminium hydride in tetrahydrofuran at -78 °C resulted in inseparable mixture of axial and equatorial alcohols **320** in 60% overall yield in a roughly one to one ratio (Scheme 137).[152]

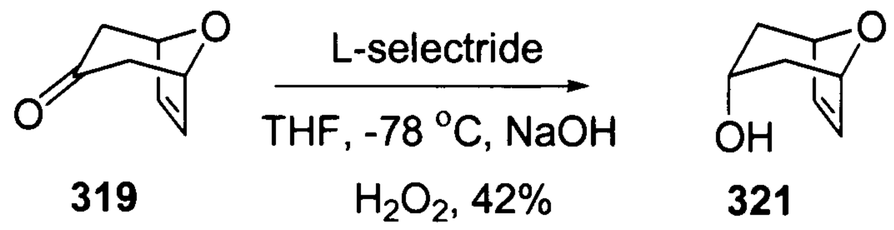


319 **320**

Scheme 137

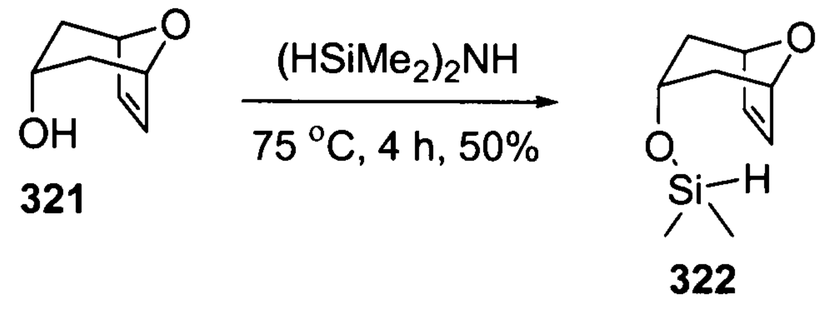
Better stereoselectivity was obtained when the reducing agent was changed to lithium tris-*sec*-butylborohydride (Scheme 138).

In the event, selective reduction of ketone **319** using lithium tris-*sec*-butylborohydride in tetrahydrofuran at -78 °C followed by oxidative workup using sodium hydroxide and hydrogen peroxide afforded known axial alcohol **321**, albeit in low yield (Scheme 138).[153] The stereochemistry of compound **321** on the basis of coupling constants in ^{1}H NMR was in good agreement with the literature.[154]



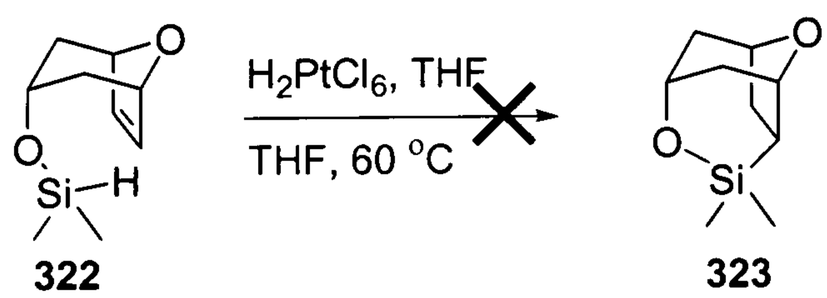
Scheme 138

Silylation of alcohol **321** using tetramethyldisilazane at 75 °C for 4 h gave silyl ether **322** as a pale yellow oil in 50% yield that was used in the next step without further purification (Scheme 139).[155]



Scheme 139

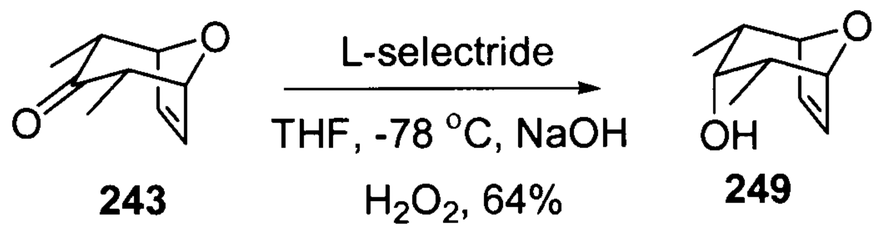
Attempted intramolecular hydrosilylation of *endo* alcohol **322** using 0.5 mol% of chloroplatinic acid in tetrahydrofuran at 60 °C proved problematic. ^{1}H NMR analysis of the crude reaction showed formation of cyclic siloxane **323**. However, an attempt to purify the crude reaction mixture by column chromatography led to decomposition of oxasilacyclopentane **323** (Scheme 140).[152]



Scheme 140

Given the results of Scheme 140, it was hoped that the diisopropylsilane derivative of **323** would be much less volatile, furthermore an alkyl substituent at the 2,4 position of the oxabicylic system should add to the stability of the subsequent oxasilacyclopentane derivatives. In order to bring these proposals into practice alcohol **249** was prepared (Scheme 141).

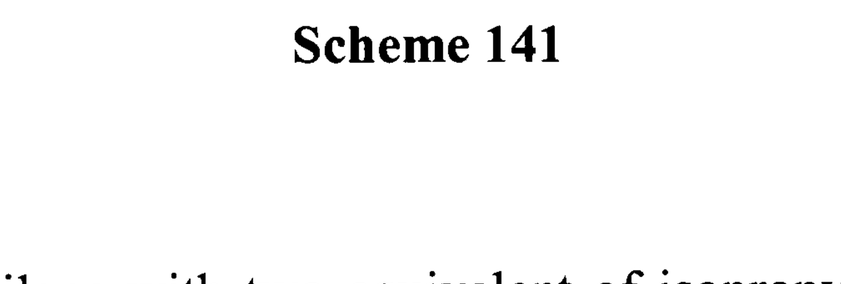
Selective reduction of ketone **243** using lithium tris-*sec*-butylborohydride in tetrahydrofuran at -78 °C followed by oxidative workup using sodium hydroxide and hydrogen peroxide, gave *endo* alcohol **249** in good yield (Scheme 141). The stereochemistry of known alcohol **249** was consistent with that reported in the literature.[152]



243 **249**

Scheme 141

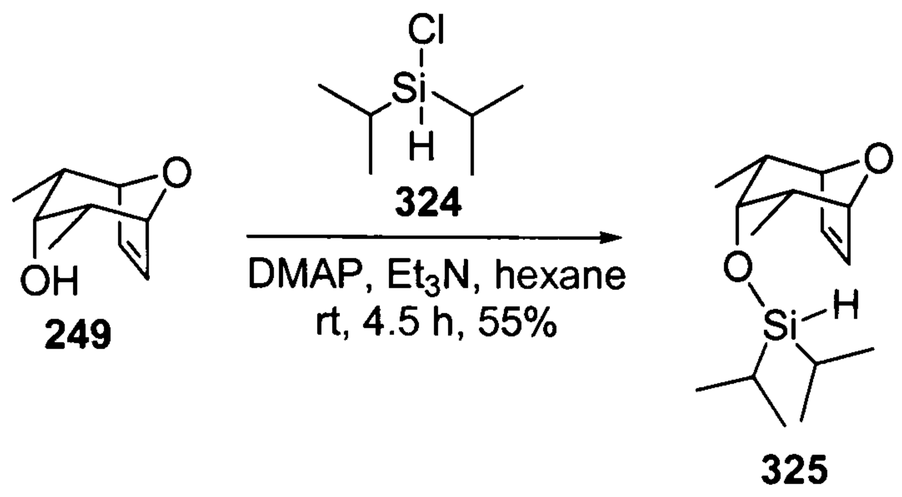
Treatment of trichlorosilane with two equivalent of isopropylmagnesium chloride in diethyl ether at room temperature for 18 h gave a residue that was purified by distillation at atmospheric pressure (101-105 °C) to afford compound **324** as a colourless oil in 33% yield (Scheme 142).[156]



324

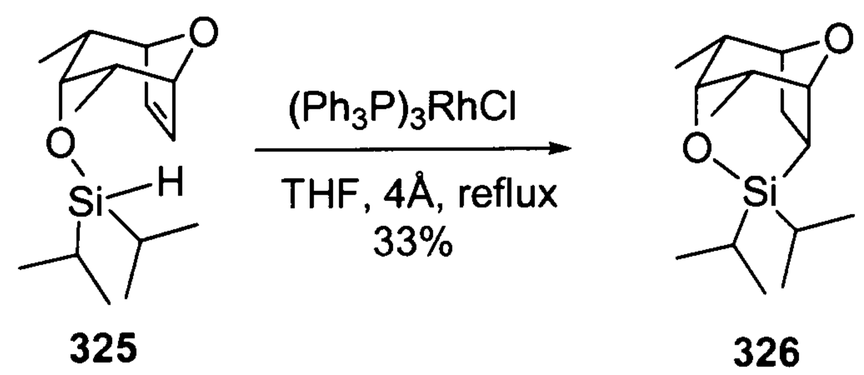
Scheme 142

Silylation of alcohol **249** was effected by using chlorodiisopropylsilane **324** and triethylamine in the presence of 4-(dimethylamino)pyridine in hexane at room temperature for 4.5 h. The crude product was stable enough for it to be purified by column chromatography (3:1 60-80 petroleum ether/diethyl ether) affording silyl ether **325** as a colourless oil in 55% yield (Scheme 143).[153]



Scheme 143

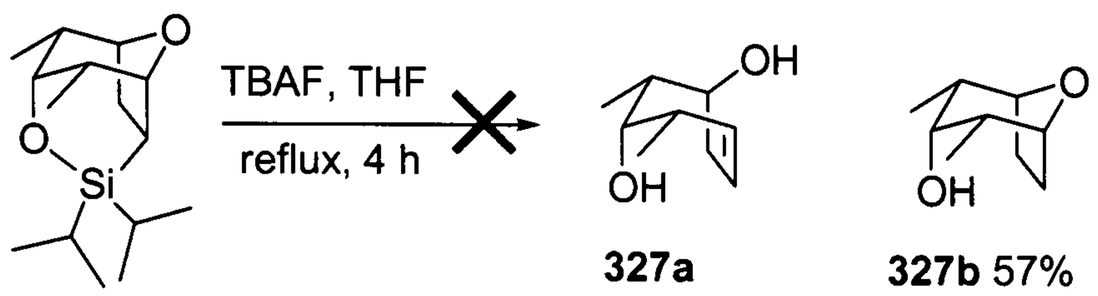
Intramolecular hydrosilylation of **325** using Wilkinson's catalyst $[Rh(PPh_3)_3]Cl$ in refluxing tetrahydrofuran for 4 h gave cyclic siloxane **326**, albeit in low yield (Scheme 144). Siloxane **326** was stable enough for it to be purified by column chromatography (hexane/diethyl ether).[153]



Scheme 144

Attempted ring opening of siloxane **326** using two equivalent of tetrabutylammonium fluoride in refluxing tetrahydrofuran yielded none of desired diol **327a**, instead

formation of alcohol **327b** was observed in 57% yield (Scheme 145). Formation of compound **327b** is attributed to protodesilylation of siloxane **326**.[157] Under these forcing conditions, it was hoped that formation of diol **327a** would be preferred.

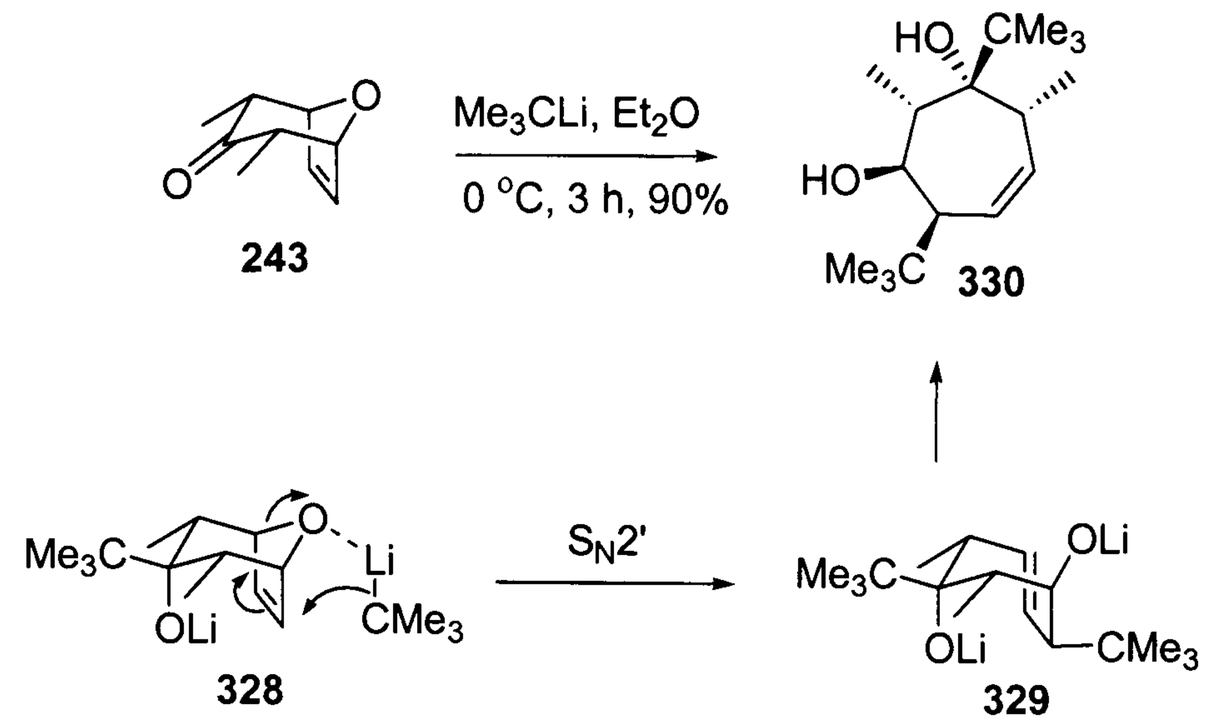


326 **327a** **327b** 57%

Scheme 145

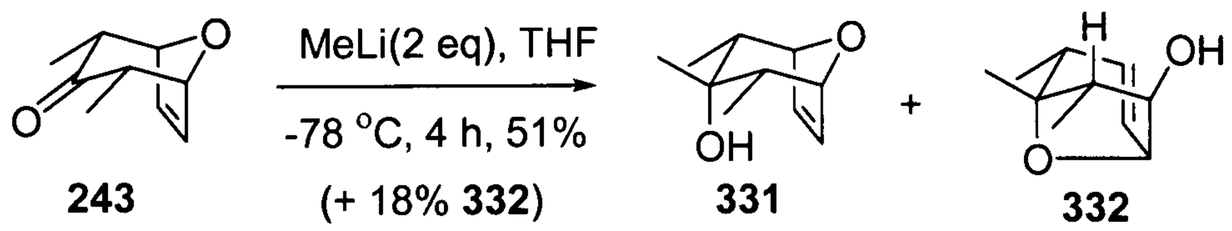
Ring opening of oxabicyclic [3.2.1] systems such as **249** by alkyl nucleophiles is well documented.[158,159,160] Oxidative cleavage of the bridging double bond can lead to polysubstituted cycloheptanediols with multiple stereocentres that could provide a new avenue to complex natural products.

For example treatment of oxabicylic ketone **243** with alkyllithium induced a ring opening reaction that led to the formation of cycloheptenediol **330** (Scheme 146). Formation of **330** was ascribed to addition of the organolithium from the equatorial direction to form **328**, followed by a second addition of organolithium reagent to the *exo* face of the double with concomitant expulsion of the bridging oxygen in an S_N2' fashion which led to **330** via **329** (Scheme 146).[154]



Scheme 146

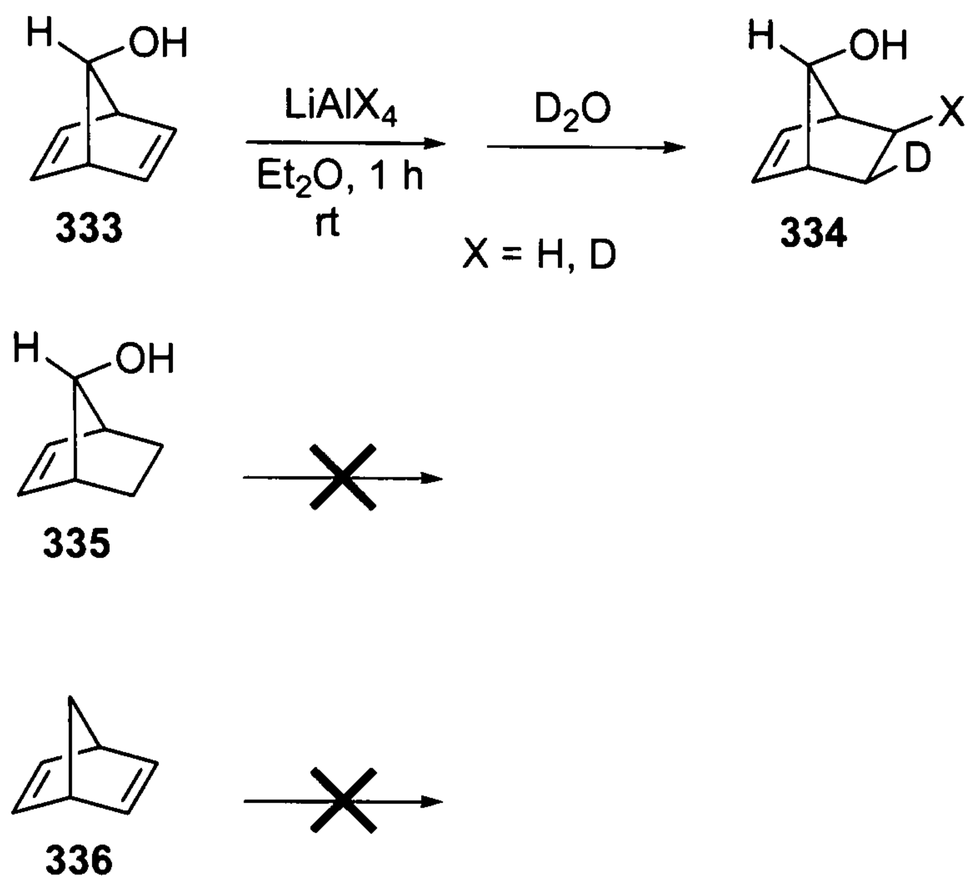
Interestingly, treatment of oxabicyclic ketone **243** with two equivalent of methyllithium in tetrahydrofuran at -78 °C gave known methylated *endo* alcohol **331**[151] in 51% yield, along with ring opened adduct **332** (Scheme 142). Formation of **332** may be attributed to formation of an intermediate similar to **328** followed by nucleophilic attack on the double bond by the axial alkoxide with concomitant ring opening of the bridging oxygen. The presence of compound **332** illustrates once more the close proximity of the axial hydroxyl group to the internal double bond in the oxabicyclic [3.2.1] system (147).



Scheme 147

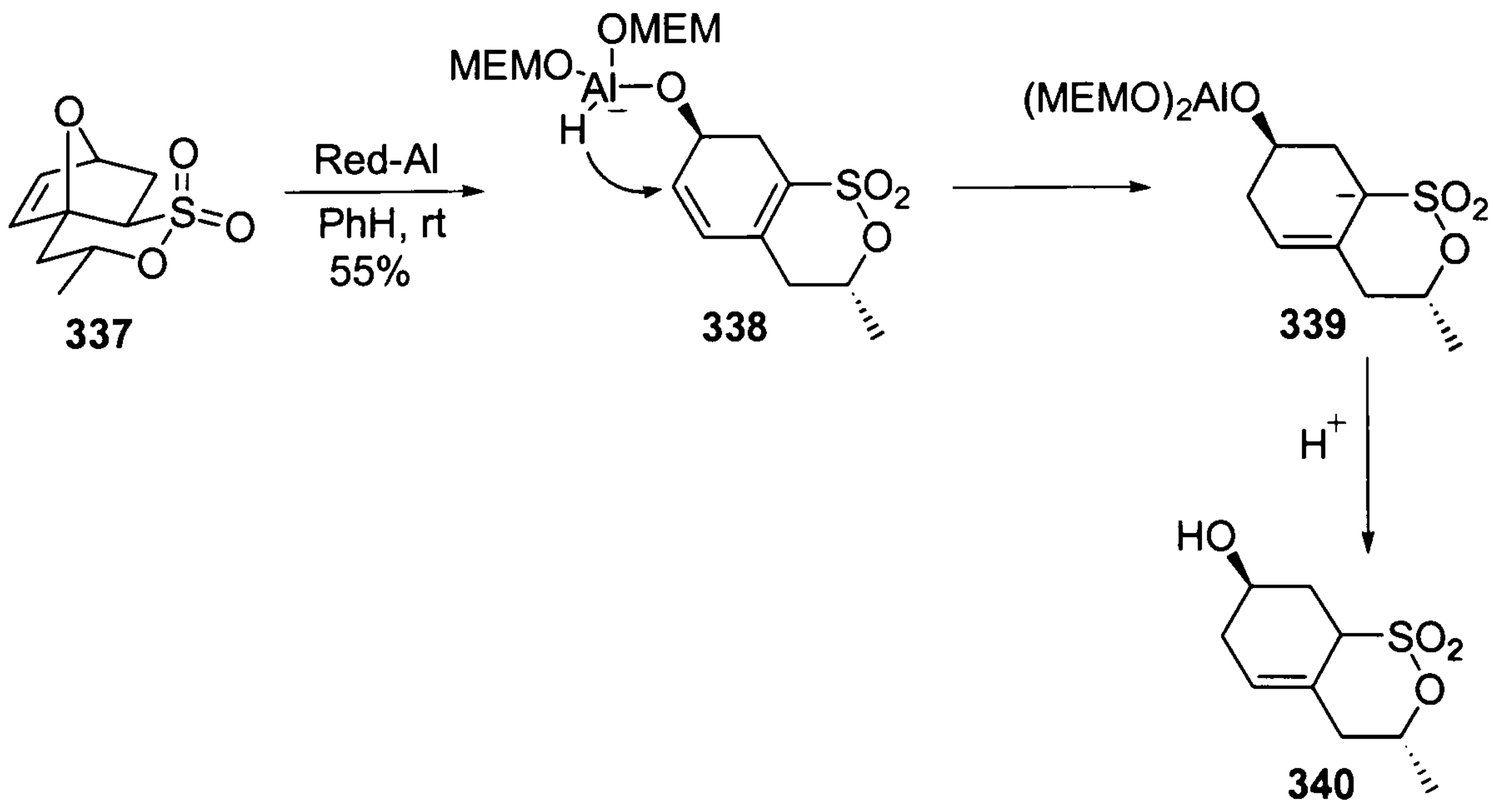
A variety of aluminium hydrides have been found to induce the reductive ring opening of [3.2.1] oxabicylic ring systems.[161] For example, Snyder reported that upon treatment with lithiumaluminium hydride 7-hydroxynorbornadiene **333** selectively underwent exo-*cis* addition to the double bond *syn* to the homoallylic hydroxyl group

to afford 7-norbornenol **334**, where as *anti*-7-norbornenol **335** and norbornadiene **336** were unreactive under same conditions (Scheme 148).[162]



Scheme 148

Furthermore, Metz reported that treatment of sultone **337** with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) resulted in initial deprotonation of **337** by Red-Al and ring opening to aluminate **338**. Intramolecular delivery of a hydride in **388** followed by protonation led to alcohol **340** (Scheme 149).[163]

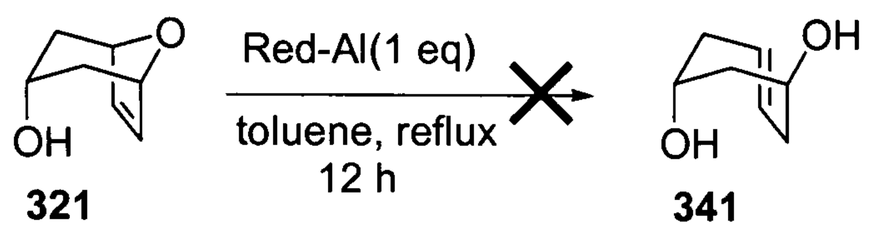


Scheme 149

4.2.1 Attempted ring opening of compound 249

It was anticipated that treatment of alcohol **321** with Red-Al could induce a ring opening reaction resulting in diol **341**.

In the event, reaction of endo alcohol **302** with Red-Al in refluxing toluene for 12 h only resulted in the recovery of starting material (Scheme 150).

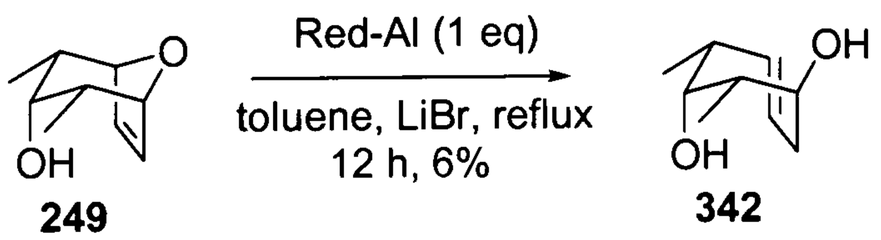


321 **341**

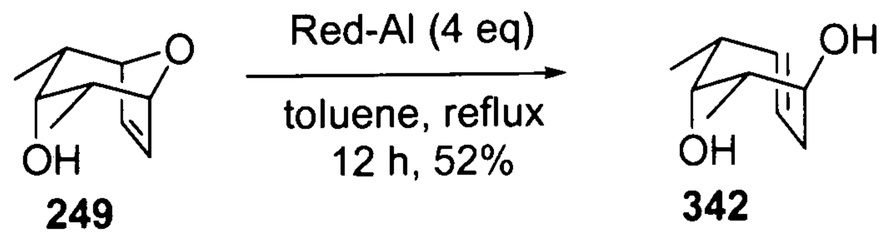
Scheme 150

However, treatment of alcohol **249** with one equivalent of Red-Al in the presence of lithium bromide in refluxing toluene for 12 h gave along with recovered starting material 6% of desired cycloheptenediol **342** (Scheme 151).

Better yields were obtained when four equivalent of Red-Al was used in the absence of lithium bromide. Under these conditions compound **342** was obtained in 52% yield (Scheme 151).



249 **342**



249 **342**

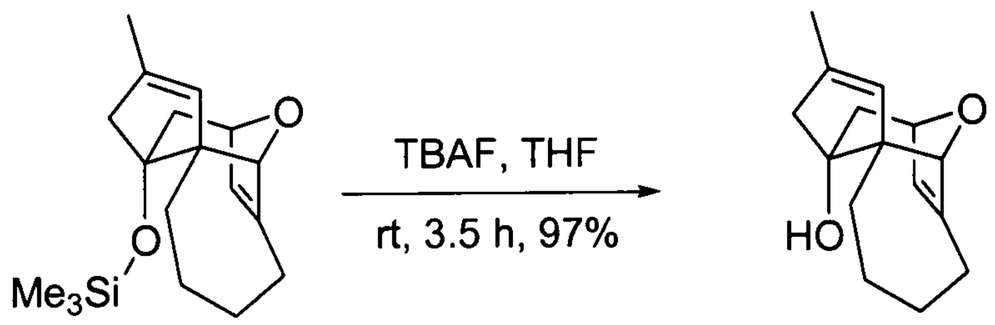
Scheme 151

4.2.2 Attempted ring opening of compound 343

Although ring opening was achieved with model alcohol **249**, it was difficult to deduce if hydroalumination had occurred from the *endo* or the *exo* face of the double bond. That said, if the reaction proceeds via an aluminate species of type **338**, then using more than one equivalent of Red-Al is likely to favour reduction from the more accessible exo face of the double bond.

The face selectivity issue should be resolved by NMR analysis in the case of tetracyclic adduct **296** due to the alkyl substituent around the internal double bond. Furthermore, stereoselective ring opening of the alcohol derived from deprotection of **296** should be favoured over alcohol **249** owing to the release in ring strain. To this end alcohol **343** was prepared.

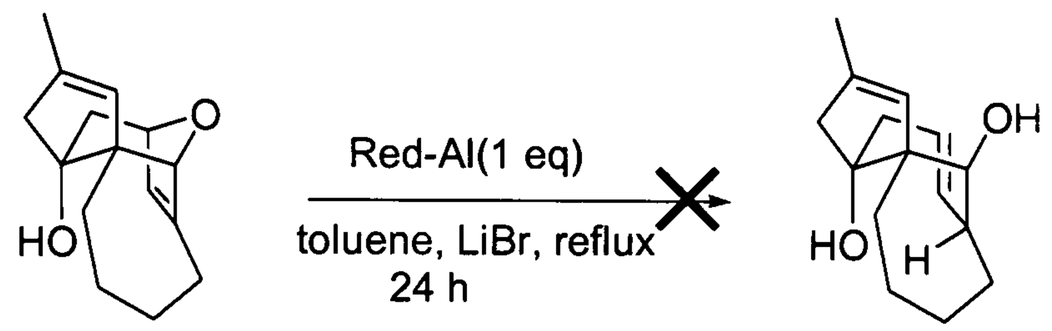
Deprotection of silyl ether **296** was effected by using tetrabutylammonium fluoride in tetrahydrofuran for 3.5 h at room temperature. Under these conditions the desired alcohol **343** was obtained as a colourless oil in excellent yield (scheme 152).



296 **343**

Scheme 152

Attempted ring opening reaction of tetracyclic alcohol **343** using Red-Al in the presence of lithium bromide in refluxing toluene for 24 h, only resulted in the recovery of starting material (Scheme 153).

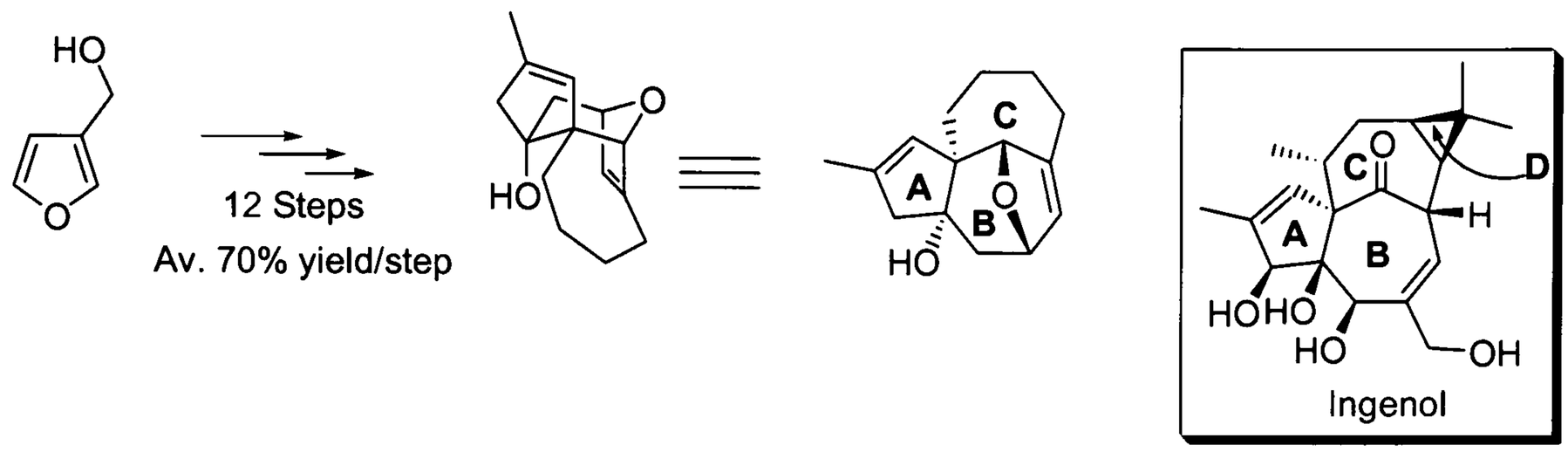


343 **344**

Scheme 153

Although the reaction was attempted only once owing to time constraints, it was evident that under these conditions stereoselective ring opening would be difficult to achieve due to the hindered nature of the axial alcohol in **343** and the bulk of the reducing agent.

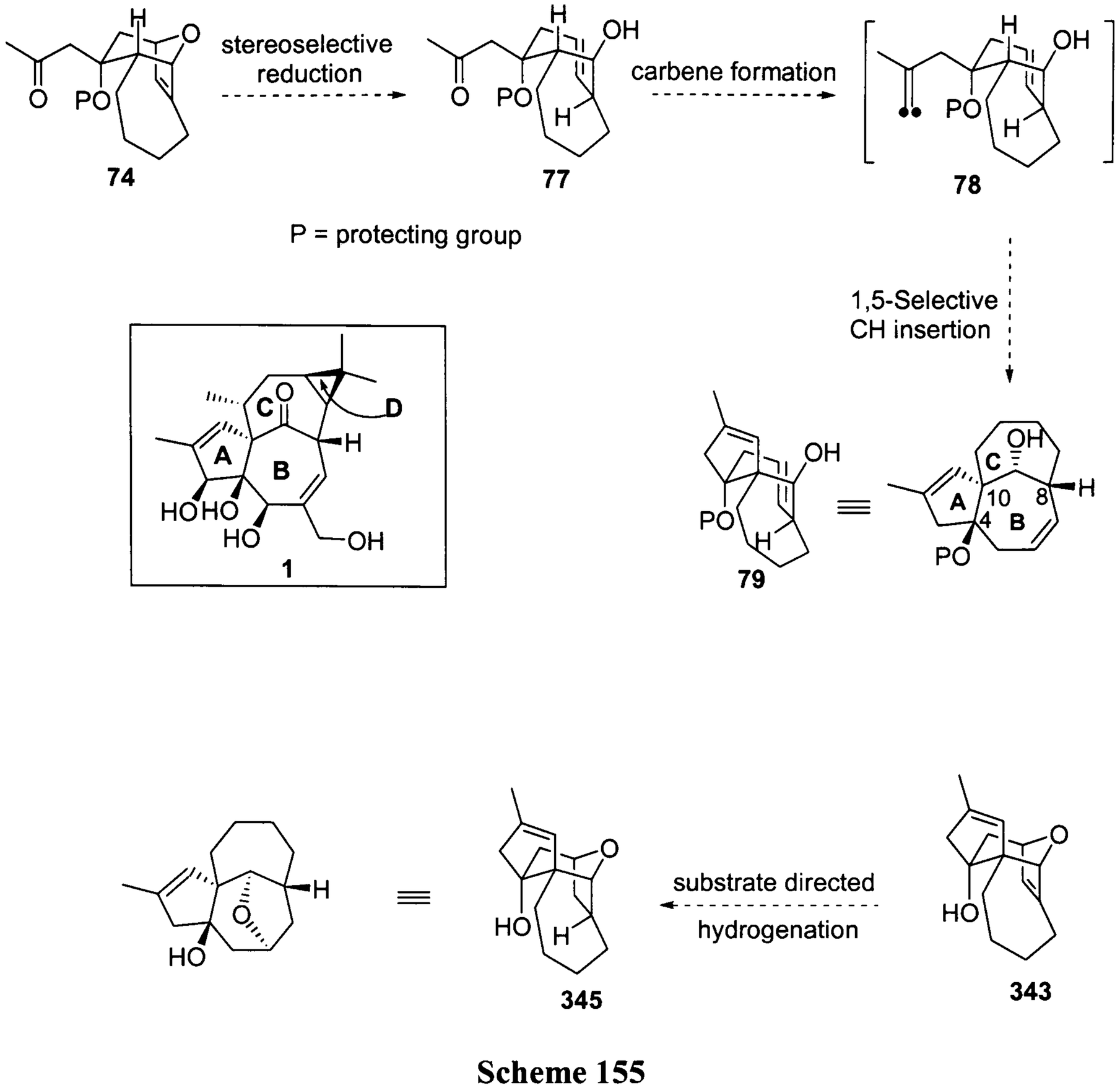
4.3.0 Conclusion and Future Work



Scheme 154

In conclusion, it has been shown that the Favorskii rearrangement is preferred over the Type-II intramolecular [4+3] cycloaddition in fluorinated alcohol solvents. An intermolecular [4+3] cycloaddition followed by intramolecular enolate alkylation to close a seven membered ring has been developed as synthetic alternative. Construction of the A-ring of ingenol is achieved via intramolecular alkylidenecarbene 1,5 C-H insertion reaction. Overall formation of the core ingenol skeleton (A,B and C rings) has been successfully accomplished (Scheme 154).

Future work in this project may include stereoselective ring opening of compound **74** prior to *in situ* generation of alkylidenecarbene **78** and selective 1,5 C-H insertion reaction to the desired alcohol **79** (Scheme 155). Substrate directed hydrogenation of **343** also offers an opprtuinity to synthesise alcohol **345**, containing the requisite *trans* arrangement in the [4.4.1] carbocyclic system of ingenol (Scheme 155).


H
O
O
PO
74
stereoselective
reduction
H
OH
O
PO
H
77
carbene formation
H
OH
PO
H
78
P = protecting group
1,5-Selective
CH insertion
C
O
D
H
A
B
HO
HO
HO
OH
1
OH
PO
H
79
OH
C
A
10
8
H
4
B
PO
H
O
HO
O
HO
H
345
substrate directed
hydrogenation
O
HO
343

Scheme 155

CHAPTER 5

Experimental

General procedures

Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Fourier transform I.R. spectrometer. ^{1}H NMR were recorded using a Bruker AM 360 MHz spectrometer in deuterochloroform referenced to TMS (0 ppm) or $CHCl_3$ (7.26 ppm). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (*J* Hz). The following abbreviations are used: s-singlet, d-doublet, dd-double doublet, t-triplet, m-multiplet. ^{13}C NMR were recorded on a Bruker AM360 spectrometer in deuterochloroform unless otherwise stated. Chemical shifts are in parts per million (δ ppm). Mass spectra were recorded by electron impact (EI) or chemical ionization (CI). High resolution mass spectra were recorded using fast atom bombardment (FAB). Melting points are uncorrected. Analytical TLC was carried out on Merck (aluminium sheets) silica gel plates using short wave (254 nm) UV light, $KMnO_4$ and anisaldehyde to visualise components. Silica gel (silica gel 60, 230-400 mesh, Merck) was used for flash column chromatography, according to the method of Still.[1]

Solvents and reagents were purified as follows:

Trifluoroethanol was distilled from calcium hydride.

Tetrahydrofuran was freshly distilled from sodium wire and benzophenone.

Diethyl ether was dried over sodium wire.

PBr_3 was purified by distillation using a high-pressure vacuum pump.

Sodium hydride was freed of mineral oil by triturating three times with 60-80 petroleum ether.

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[1] Still, W.C; Kahn, M.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *43*, 2923.

DMF was purified by distillation from calcium hydride under reduce pressure.

DMSO was purified by distillation from calcium hydride under reduce pressure.

Dibromomethane was purified by distillation from calcium hydride under reduce pressure.

Dichloromethane was freshly distilled from calcium hydride.

Dicyclohexylamine was purified by distillation from calcium hydride.

All other commercially available reagents were used as received

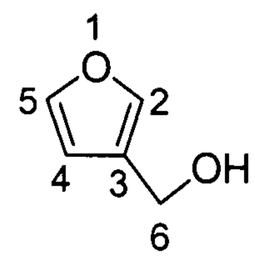
Cooling mixtures were obtained as follows:

0 °C: ice/water.

-5 °C to –78 °C: acetone/dry ice.

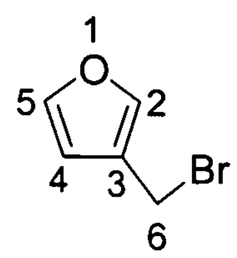
All reactions were carried out in oven-dried glassware under nitrogen or argon atmosphere unless otherwise stated.

3-Furylmethanol (136)[68]



To a stirred suspension of $LiAlH_4$ (6.10 g, 166 mmol) in diethyl ether (80 mL) was added dropwise so as to cause a gentle reflux, a solution of 3-furoic acid (15.1 g, 134 mmol) in diethyl ether (60 mL) at 0 °C. The mixture was stirred for 24 h at room temperature and water (250 mL) was cautiously added at 0 °C followed by 10% H_2SO_4 (300 mL). The aqueous layer was extracted with diethyl ether (3 x 250 mL). The combined ethereal layer was washed with brine (250 mL) and dried over $MgSO_4$. Concentration of the organic layer in vacuo gave a residue that was purified by distillation using Kugelrohr apparatus (2mm Hg / 44-80 °C, with decreasing pressure) to afford alcohol **136** (10.8 g, 82%, lit.[68] 91%) as a colourless oil; R_f 0.43 (3:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 3505 (*br*), 2938, 2866, 1070; δ_H (360 MHz; $CDCl_3$) 2.47 (1H, br, O-H), 4.42 (2H, s, 6-H), 6.33 (1H, dd, J = 1.8 and 0.9 Hz, 4-H), 7.31 (1H, dt, J = 1.8 and 0.9 Hz, 2-H), 7.45 (1H, t, J = 1.8 Hz, 5-H); δ_C (90 MHz, $CDCl_3$) 58.6 (t, 6-C), 112.1 (d, 4-C), 128.1 (s, 3-C), 139.5 (d, 2-C), 143.5 (d, 5-C); *m/z* (EI) 98 (M^+; 100%), 97 (56.1), 81 (31.1), 69 (82.2), 57 (35.1).

3-Bromomethylfuran (137)[69]



Method 1

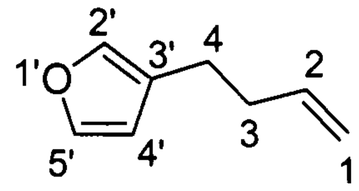
To a solution of alcohol **136** (2.50 g, 25.5 mmol) in THF (60 mL) maintained at 0 °C was added phosphorous tribromide (2.40 g, 8.90 mmol). The reaction was brought to room temperature and stirred for 18 hours. The reaction was quenched with water (25 mL) and extracted with diethyl ether (3 x 100 mL). The combined ethereal layer was washed with saturated aqueous $NaHCO_3$ (40 mL), brine (50 mL) and dried over $MgSO_4$. The organic layer was concentrated in vacuo to afford bromide **137** (3.50 g, 87%) that was used without further purification.

Method 2

To a stirred solution of alcohol **136** (4.01 g, 40.0 mmol) and carbon tetrabromide (16.0 g, 46.0 mmol) in DCM (50 mL) at 0 °C was added portionwise triphenyl phosphine (16.5 g, 63.0 mmol). The mixture was stirred for a further 2 h and the solvent removed in vacuo. Diethyl ether (50 ml) was added and the mixture was filtered. The filtered cake was washed with diethyl ether (3x 50mL). The combined washings were concentrated in-vacuo to give a residue that was purified by column chromatography (5:1 hexane/ethylacetate) to afford bromide **137** (4.5 g, 70%, lit.[69] 91%) as a colourless oil; R_f 0.54 (5:1 hexane/ethylacetate); υ_{max} (neat)/cm^{-1} 2938, 2866, 1502, 750; δ_H (360 MHz; $CDCl_3$) 4.43 (2H, s, 6-H), 6.50 (1H, dd, J = 1.8 and 0.9 Hz, 4-H), 7.31 (1H, dt, J = 1.8 and 0.9 Hz, 2-H), 7.41 (1H, t, J = 1.8 Hz, 5-H); δ_C (90 MHz,

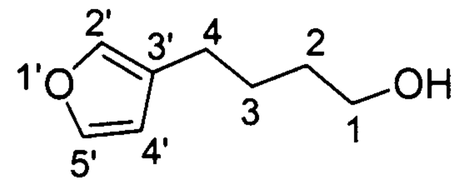
$CDCl_3$) 24.0 (t, 6-C), 111.3 (d, 4-C), 123.0 (s, 3-C), 141.2 (d, 2-C), 144.2 (d, 5-C); *m/z* (EI) 161 (M^+; 100%), 135(77), 105 (39.3), 69 (82.2), 81 (55.1), 55 (90.6).

3'-(But-4-enyl)-furan (138)[68]



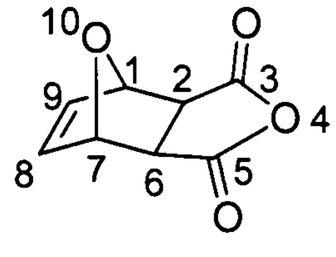
To a solution of bromide **137** (1.70 g, 10.6 mmol) in THF (20 mL) was added allylmagnesium chloride (THF, 20 mL, 2 M, 40.0 mmol) at 0 °C. The mixture was stirred for 4 h while warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (80 mL) and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were washed with brine (30 mL) and dried over $MgSO_4$. Concentration of the organic layer in vacuo afforded alkene **138** (0.46 g, 40%) that was used without further purification; R_f 0.61 (6:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2958, 2866, 1755, 1450; δ_H (360 MHz; $CDCl_3$) 2.22-2.28 (2H, m, 3-H), 2.44 (2H, t, J = 6.1 Hz, 4-H), 4.91-4.96 (2H, m, 1-H), 5.73-5.78 (1H, m, 2-H), 6.20 (1H, dd, J = 1.8 and 0.9 Hz, 4'-H) 7.15 (1H, dt, J = 1.8 and 0.9 Hz, 2'-H), 7.26 (1H, t, J = 1.8 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.7 (t, 3-C), 34.1 (t, 4-C), 111.4(d, 4'-C), 115.4 (t, 1-C), 124.9 (s, 3'-C) 139.3 (d, 2'-C), 143.1 (d, 5'-C); *m/z* (EI) 122 (M^+; 11.2%), 88 (44.5), 81 (100), 67 (44.2), 49 (59.9).

4-(3'-Furyl)-butan-1-ol (139)[68]



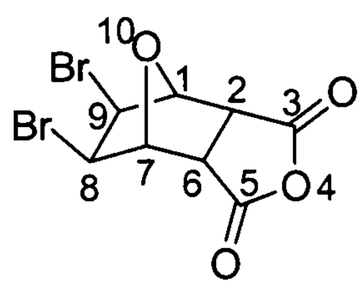
To a solution of disiamylborane prepared as follows: to a stirred solution of a borane-dimethylsulfide complex (10.2 mL, 204 mmol) in THF (60 mL) was added 2-methyl-2-butene (102 mL, 102 mmol) at 0 °C. The mixture was stirred for 1 h and alkene **138** (5.01 g, 51.0 mmol) was added. The resulting mixture was then stirred for a further 1 h. The reaction was quenched cautiously with NaOH (70 mL, 3 M, 210 mmol) followed by 27% H_2O_2 (33 mL, 262 mmol). The mixture was stirred for 1 h and then diluted with water (50 mL). The aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic layer was dried ($MgSO_4$) and concentrated in vacuo to give organic residue that was purified by column chromatography (3:7 ethyl acetate/hexane) to give alcohol **139** (3.3 g, 45%; lit.[68] 49%) as colourless oil; R_f 0.44 (1:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 3350 (*br*), 2936, 2865, 1501; δ_H (360 MHz; $CDCl_3$) 1.30-1.41 (1H, m, O-H), 1.62-1.66 (4H, m, 2,3-H), 2.47 (2H, t, J = 6.8 Hz, 5-H), 3.68 (1H, t, J = 6.1 Hz, 1-H), 6.20 (1H, dd, J = 1.8 and 0.9 Hz, 4'-H) 7.15 (1H, dt, J = 1.8 and 0.9 Hz, 2'-H), 7.26 (1H, t, J = 1.8 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 26.8 (t, 4-C), 28.4 (t, 3-C), 34.6 (t, 2-C), 65.0 (t, 1-C), 115.4 (d, 4'-C), 124.9 (s, 3'-C) 139.3 (d, 2'-C), 143.1 (d, 5'-C); *m/z* (EI) 140 (M^+; 52.1%), 94 (66.2), 81 (100), 69 (42.4), 53 (55.7).

4,10-Dioxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (142)[71]

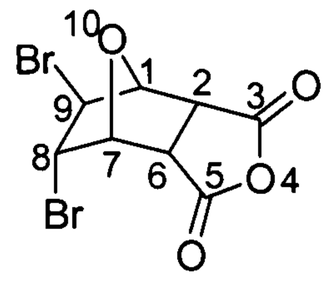


To a stirred solution of maleic anhydride (50.0 g, 507 mmol) in diethyl ether (250 mL) was added furan (69.0 g, 1.01 mol) at room temperature. The reaction mixture was stirred overnight at room temperature and then filtered under suction to obtained the *title compound* was as a solid (78 g, 93%); υ_{max} (neat)/cm^{-1} 2964, 2140, 1705; δ_H (360 MHz; $CDCl_3$) 3.20 (2H, s, 2,6-H), 5.48 (2H, s, 1,7-H), 6.60 (2H, s, 8,9-H); δ_C (90 MHz, $CDCl_3$) 49.0 (d, 2,6-C), 82.6 (d, 1,7-C), 137.4 (d, 8,9-C), 170.3 (s, 3,5-C); *m/z* (EI) 166 (M^+; 35%), 94 (100), 68 (63).

8,9-*cis*-Dibromo-4,10-dioxa-tricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione (143a) and 8,9-*trans*-Dibromo-4,10-dioxa-tricyclo[5.2.1.$0^{2,6}$]decane-3,5-dione (143b)[72]



143a



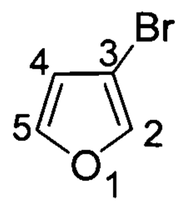
143b

A solution of adduct **142** (78.0 g, 470 mmol) in DCM (2.3 L) was treated with bromine (24.0 mL, 470 mmol) at room temperature. The reaction mixture was vigorously stirred overnight, by which time the bromine colour had disappeared and a solid precipitate was formed. The reaction mixture was filtered and washed with DCM

(100 mL) to give compound **143a** (35.0 g, 23%, lit.[72] 35%) as a solid. The mother liquor was concentrated to dryness to give compound **143b** (117 g, 76%, lit.[72] 59%). Analytical data for **143a**: υ_{max} (neat)/cm^{-1} 2947, 1695, 760; δ_H (360 MHz; $CDCl_3$) 3.66 (2H, s, 2,6-H), 4.84 (2H, s, 8,9-H), 4.97 (2H, s, 1,7-H); δ_C (90 MHz, $CDCl_3$) 49.3 (d, 2,6-C), 53.0 (d, 8,9-C), 87.8 (d, 8,9-C), 170.1 (s, 3,5-C); *m/z* (EI) 326 (M^+; 35%), 94 (100), 68 (63).

Analytical data for **143b**: υ_{max} (neat)/cm^{-1} 2958, 1702, 772; δ_H (360 MHz; $CDCl_3$) 3.88 (2H, q, J = 10.0 and 7.44 Hz, 2,6-H), 4.50-4.53 (2H, m, 8,9-H), 5.01 (1H, s, 1-H), 5.19 (1H, d, J = 5.0 Hz, 7-H); δ_C (90 MHz, $CDCl_3$) 47.2 (d), 49.3 (d), 52.7 (d), 83.5 (d), 87.1 (d), 170.8 (s), 172.2 (s); *m/z* (EI) 326 (M^+; 38%), 94 (71), 68 (100).

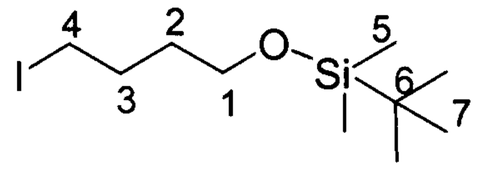
3-Bromo-furan (144)



A mixture of brominated adducts **143a** and **143b** (58.3 g, 179 mmol) and quinoline (85 mL, 715 mmol) was heated to 230 °C over 2 h. Crude material of the desired compound was collected at this temperature. The crude distillate was dried over sodium sulphate and redistilled from potassium carbonate (15 g) through a column (40 cm) to give the *title compound* (11.7 g, 45%, lit.[73] 60%) as a pale yellow oil. Analytical data agrees with literature;[73] υ_{max} (neat)/cm^{-1} 3001, 2973, 1643, 1046, 788; δ_H (360 MHz; $CDCl_3$) 6.47 (1H, dd, J = 1.9 and 0.7 Hz, 4-H), 7.39 (1H, dt, J = 1.9 and

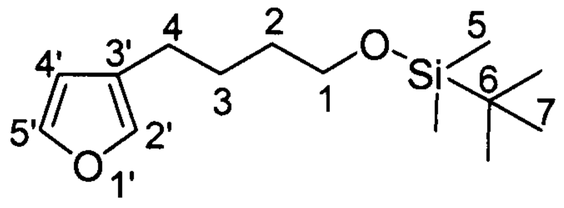
0.7 Hz, 2-H), 7.46 (1H, dd, J = 1.9 and 0.7 Hz, 5-H); δ_C (90 MHz, $CDCl_3$) 100.2 (s, 3-C), 113.8 (d, 4-C), 141.4 (d), 143.9 (d); *m/z* (EI) 147 (M^+; 5%), 129 (100), 69 (67).

tert-Butyl-(4-iodobutoxy) dimethylsilane (145)[74]

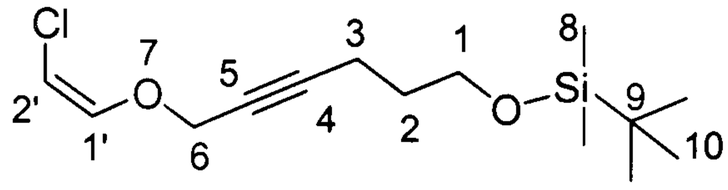


A mixture of *tert*-buthyldimethylsilyl chloride (151 g, 20.0 mmol), sodium iodide (6.02 g, 40.0 mmol) and tetrahydrofuran (4.10 mL, 49.2 mmol) in CH_3CN (40 mL) were heated to 55 °C for 14 h. The reaction was cooled to room temperature and water (120 mL) was added. The aqueous layer was extracted with pentane/diethyl ether (9:1, 3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the *title compound* (4.9 g, 70%) as a yellow liquid that was used without further purification. R_f 0.65 (7:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2941, 1020, 695; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 5-H), 0.84 (9H, s, 7-H), 1.54-1.60 (2H, m, 2-H), 1.84-1.89 (2H, m, 3-H), 3.17 (2H, t, J = 7.0 Hz, 4-H), 3.58 (2H, t, J = 6.2 Hz, 1-H); δ_C (90 MHz, $CDCl_3$) -4.9 (q, 5-C), 7.5 (t, 4-C), 18.7 (s, 6-C), 26.3 (q, 7-C), 30.6 (t), 33.9 (t), 62.3 (t, 1-C); *m/z* (EI) 314 (M^+; 33%), 199 (43), 131 (100).

tert-Butyl(4-(furan-3'-yl)butoxy)dimethylsilane (146) and (_Z_)-_tert_-Butyl[6-(2'-chlorovinyloxy)hex-4-ynloxy]dimethylsilane (153)



146

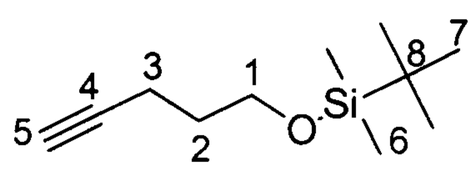


153

To a mixture of anhydrous $CrCl_3$ (11.1 mg, 70.0 μmol), Mn powder (229 mg, 4.20 mmol) and TMSCl (530 μL, 4.20 mmol) in THF (8 mL) was added a solution of propargyl ether **152** (360 mg, 1.01 mmol) in THF (2 mL). The reaction mixture was heated at 60 °C for 15 h, cooled and quenched with water (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give a crude residue that was purified by column chromatography (5% diethyl ether in hexane) to give first compound **146** (75 mg, 28%) as a colourless oil, followed by compound **153** (10 mg, 3.5%) as a pale yellow oil. Analytical data for compound **146**: R_f 0.56 (5% diethyl ether in hexane); υ_{max} (neat)/cm^{-1} 2954, 1651, 1055; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 5-H), 0.84 (9H, s, 7-H), 1.50-1.57 (4H, m, 2,3-H), 2.38 (2H, t, J = 7.0 Hz, 4-H), 3.58 (2H, t, J = 6.1 Hz, 1-H), 6.22 (1H, dd, J = 1.7 and 0.8 Hz, 4'-H), 7.16 (1H, dt, J = 1.7 and 0.8 Hz, 2'-H), 7.29 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) -4.9 (q, 5-C), 18.8 (s, 6-C), 24.9 (t), 26.4 (q, 7-C), 26.7 (t), 31.8 (t, 4-C), 63.5 (t, 1-C), 111.4 (d, 4'-C), 125.5 (s, 3'-C), 139.2 (d, 2'-C), 143.0 (d, 5'-C); _m/z_ (EI) 254 (M^+; 68%), 139 (100), 130 (70); HRMS calcd for $C_{14}H_{26}O_2SiNa^+$ 277.1460, found 277.1458.

Analytical data for compound **153**: R_f 0.38 (5% diethyl ether in hexane); υ_{max} (neat)/cm^{-1} 2949, 2117, 1020, 811; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 8-H), 0.84 (9H, s, 10-H), 1.64-1.68 (2H, m, 2-H), 1.94 (2H, t, J = 6.6 Hz, 3-H), 3.62 (2H, t, J = 6.0 Hz, 1-H), 4.44 (2H, t, J = 2.2 Hz, 6-H), 5.17 (1H, d, J = 4.4 Hz, 2'-H), 6.47 (1H, d, J = 4.4 Hz, 1'-H); δ_C (90 MHz, $CDCl_3$) -5.0 (q, 8-C), 15.6 (t, 3-C), 18.9 (s, 9-C), 26.4 (q, 10-C), 31.3 (t, 2-C), 61.9 (t), 62.8 (t), 76.1 (s), 89.3 (s), 97.1 (d, 2'-C), 144.5 (d, 1'-C); *m/z* (EI) 288 (M^+; 100%), 253 (30), 138 (58); HRMS calcd for $C_{14}H_{25}{}^{35}ClO_2SiNa^+$ 311.0121, found 311.0120.

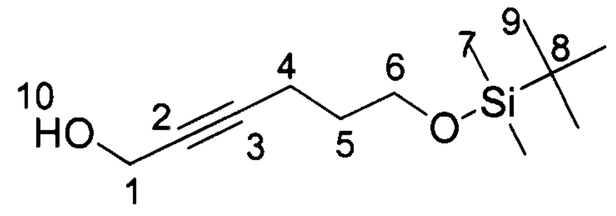
tert-Butyl dimethyl(pent-4-ynyloxy)silane (149)[81]



To a solution of pent-4-yn-1-ol (5.01 g, 59.4 mmol), triethylamine (14.2 mL, 71.3 mmol) and DMAP (730 mg, 6.02 mmol) in DCM (30 mL) was added *tert*-buthyldimetylsilyl chloride (9.90 g, 65.4 mmol) at 0 °C. The mixture was stirred for 12 h and then quenched with aqueous NH_4Cl (30 mL). The organic solution was separated, dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by flash column chromatography (4:1 hexane/diethyl ether) to afford the *title compound* (9.4 g, 80%) as a colourless oil; R_f 0.44 (8:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 3325, 2910, 2112, 1009; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 6-H), 0.84 (9H, s, 7-H), 1.64-1.67 (2H, m, 2-H), 1.87 (1H, t, J = 2.7 Hz, 5-H), 2.22-2.30 (2H, m, 3-H), 3.64 (2H, t, J = 6.0 Hz, 1-H); δ_C (90 MHz, $CDCl_3$) -5.0 (q, 6-C), 15.2 (t, 3-C), 18.7 (s, 8-C), 26.1 (q, 7-C), 31.9 (t, 2-C), 61.8 (t, 1-C), 68.6 (s, 4-C), 84.6 (d, 5-

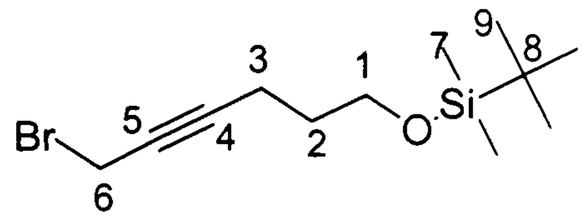
C); *m/z* (EI) 198 (M^+; 45%), 180 (47), 83 (100); HRMS calcd for $C_{11}H_{22}OSiNa^+$ 198.3116, found 198.3113

6-(*tert*-Butyldimethylsilyloxy)hex-2-yn-1-ol (150)



To a solution of **149** (5.01 g, 25.3 mmol) in THF was added, *n*-BuLi (2.5 M, 12.1 mL, 27.8 mmol) at -78 °C. After 10 min paraformaldehyde (4.10 g, 126.3 mmol) was added in one portion. The reaction mixture was stirred for 10 min at -78 °C and then brought to room temperature and stirred for a further 20 min. The reaction was quenched with saturated solution of NH_4Cl (30 mL) and extracted with diethyl ether (3 x 50 mL). The ethereal layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give compound **150** (6.3 g, 85%) as a yellow liquid that was used without further purification; R_f 0.46 (5:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3552, 2950, 2117, 1019; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 7-H), 0.84 (9H, s, 9-H), 1.46 (1H, s, 10-H), 1.64-1.67 (2H, m, 5-H), 2.43-2.48 (2H, m, 4-H), 3.62 (2H, t, J = 6.0 Hz, 6-H), 4.19 (2H, t, J = 2.1 Hz, 1-H); δ_C (90 MHz, $CDCl_3$) -5.0 (q, 7-C), 15.6 (t, 4-C), 18.7 (s, 8-C), 26.3 (q, 9-C), 32.0 (t, 5-C), 51.8 (t, 1-C), 61.9 (t, 6-C), 78.8 (s, 2-C), 86.5 (s, 3-C); *m/z* (EI) 228 (M^+; 33%), 113 (45), 97 (100); HRMS calcd for $C_{12}H_{24}O_2SiNa^+$ 251.3151, found 251.3149.

(6-Bromo-hex-4-ynyloxy)-*tert*-butyldimethylsilane (151)



To a stirred solution of alcohol **150** (6.10 g, 26.3 mmol) in THF (50 mL) at 0 °C was added phosphorus tribromide (900 μL, 9.10 mmol). After addition was completed, the mixture was allowed to warm to room temperature while stirring for 2 h. The reaction was quenched with water (15 mL), followed by extraction with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give a residue that was purified by flash column chromatography (10:1 hexane/diethyl ether) to give bromide **151** (5.3 mg, 69%) as a colourless oil; R_f 0.40 (10:1 hexane/diethyl ether); υ_{max} (neat)/cm^{-1} 2943, 2115, 1010, 725; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 7-H), 0.84 (9H, s, 9-H), 1.64-1.68- (2H, m, 2-H), 2.25-2.30 (2H, m, 3-H), 3.63 (2H, t, J = 6.0 Hz, 1-H), 3.86 (2H, t, J = 2.2 Hz, 6-H); δ_C (90 MHz, $CDCl_3$) -4.9 (q, 7-C), 16.6 (t, 3-C), 16.9 (t, 6-C), 19.5 (s, 8-C), 27.1 (q, 9-C), 32.5 (t, 2-C), 62.6 (t, 1-C), 76.6 (s, 5-C), 89.0 (s, 4-C); *m/z* (EI) 291 (M^+; 43%), 176 (60), 96 (100); HRMS calcd for $C_{12}H_{23}{}^{79}BrOSiNa^+$ 313.0137, found 313.0140.

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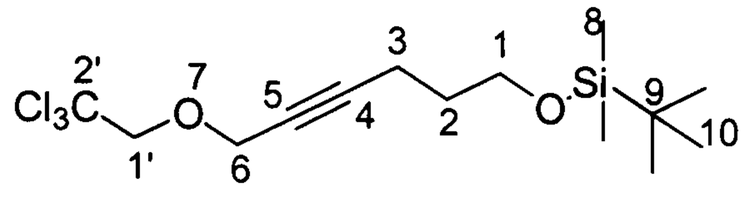
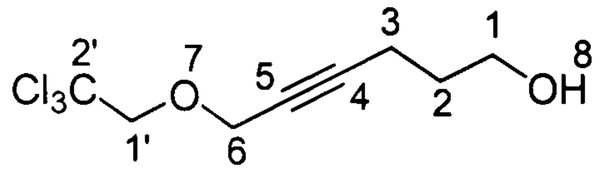
tert-Butyldimethy[6-(2',2',2'-trichloroethoxy)hex-4-ynyloxy]silane (152)



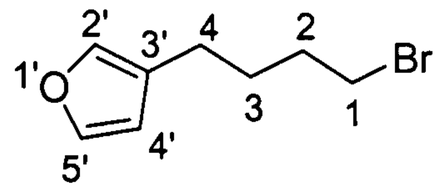
To a stirred solution of 2,2,2-trichloro ethanol (2.20 mL, 23.0 mmol) and *n*-Bu_4NI (566 mg, 1.50 mmol) in DCM (23 mL) was added drop-wise an aqueous solution of NaOH (1.70 M, 39.1 mmol) at 0 °C. After 10 min at 0 °C, a solution of compound **151** (6.1 g, 23 mmol) in DCM (10 mL) was added and the reaction mixture was stirred at room temperature for 2 d. The organic layer was separated and the aqueous layer extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow residue. The crude reaction was purified by column chromatography (10% ethyl acetate in 60-80 petroleum ether) to give compound **152** (5.3 g, 64%) as a pale yellow oil; R_f 0.50 (10% ethyl acetate in 60-80 petroleum ether); υ_{max} (neat)/cm^{-1} 2955, 2113, 1019, 725; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s, 8-H), 0.84 (9H, s, 10-H), 1.64-1.66 (2H, m, 2-H), 2.26-2.31 (2H, m, 3-H), 3.63 (2H, t, J = 6.0 Hz, 1-H), 4.10 (2H, s, 1'-H), 4.38 (2H, t, J = 2.2 Hz, 6-H); δ_C (90 MHz, $CDCl_3$) -4.9 (q, 8-C), 14.2 (t, 3-C), 18.8 (s, 9-C), 24.9 (q, 10-C), 30.5 (t, 2-C), 59.0 (t), 60.5 (t), 73.5 (s), 74.9 (s), 80.1 (t, 1'-C), 87.4 (s, 2'-C); *m/z* (EI) 358 (M^+; 25%), 242 (100), 241 (60), 116 (35); HRMS calcd for $C_{14}H_{25}{}^{35}Cl_3O_2SiNa^+$ 381.1137, found 381.1129.

6-(2',2',2',-Trichloroethoxy)hex-4-yn-1-ol (154)



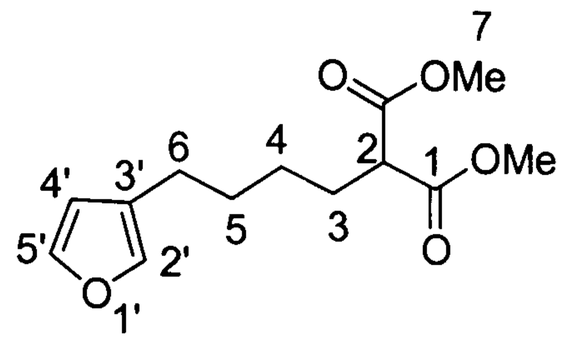
To a solution of alkyne **152** (5.3 g, 0.18 M, 20.5 mmol) in THF (50 mL) was added TBAF (41.1 mL, 1.0 M, 41.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 d, before quenching with water (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (1:1 60-80 petroleum ether/ethyl acetate) to give alcohol **154** (2.0 g, 38%) as a colourless oil; R_f 0.28 (1:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 3561, 2924, 2122, 735; δ_H (360 MHz; $CDCl_3$) 1.36 (1H, s, 8-H), 1.69-1.74 (2H, m, 2-H), 2.28-2.31 (2H, m, 3-H), 3.63-3.65 (2H, m, 1-H), 4.06 (2H, s, 1'-H), 4.34 (2H, t, J = 2.2 Hz, 6-H); δ_C (90 MHz, $CDCl_3$) 15.7 (t, 3-C), 31.5 (t, 2-C), 60.4 (t), 62.0 (t), 75.4 (s), 81.6 (t, 1'-C), 88.2 (s), 97.1 (s, 2'-C); *m/z* (EI) 244 (M^+; 100%), 227 (40), 127 (60); HRMS calcd for $C_8H_{11}{}^{35}Cl_3O_2Na^+$ 267.2341, found 267.2336.

4-(3'-Furyl)-1-bromobutane (155)



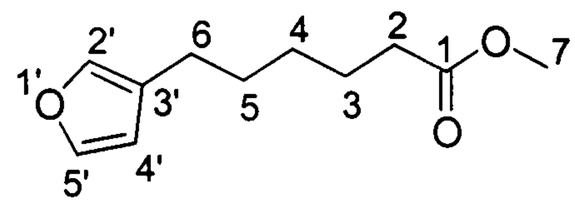
To a stirred solution of alcohol **139** (9.21 g, 50.0 mmol) and carbon tetrabromide (12.5 g, 112 mmol) in DCM (30 mL) at 0 °C was added portionwise triphenylphosphine (13.2 g, 115 mmol). After addition was completed, the mixture was allowed to warm to room temperature while stirring for 2h. The reaction was quenched with water (20 mL), followed by extraction with DCM (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (8:1 60-80 petroleum ether/diethyl ether) to afford bromide **155** (1.0 g, 89%) as a pale yellow oil; R_f 0.55 (8:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2937, 2862, 1501, 600; δ_H (360 MHz; $CDCl_3$) 1.76-1.79 (1H, m, 3-H), 1.94-1.98 (2H, m, 3-H), 2.51 (2H, t, J = 7.5 Hz, 4-H), 3.48 (1H, t, J = 6.7 Hz, 1-H), 6.32 (1H, dd, J = 1.7 and 0.9 Hz, 4'-H) 7.28 (1H, dt, J = 1.7 and 0.9 Hz, 2'-H), 7.41 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.3 (t, 4-C), 28.9 (t, 3-C), 33.3 (dd, 1,2-C), 115.4 (d, 4'-C), 124.9 (s, 3'-C) 139.3 (d, 2'-C), 143.1 (d, 5'-C); *m/z* (EI) 204 (M^+; 10.5%), 123 (28.5), 81 (100), 67 (10.8); HRMS calcd for $C_8H_{12}OBr$ 204.007, found 204.006.

2-(6-Furyl-3'-yl-butyl)-malonic acid dimethyl ester (157)



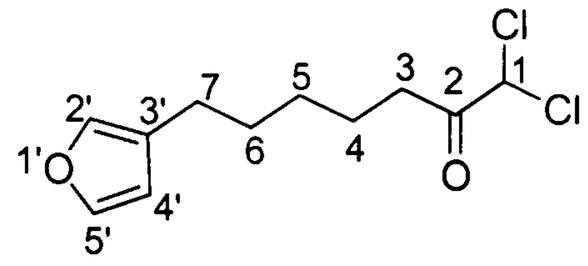
To a solution of NaH (1.40 g, 1.35 mmol) in DMF (30 mL) and THF (86 mL) at 0 °C was added dimethylmalonate (16.0 mL, 143 mmol). The mixture was allowed to stir while warming to room temperature for 15 minutes and then bromide **155** (5.80 g, 28.6 mmol) was added. The mixture was refluxed for 1.5 h then cooled and concentrated to give a residue that was diluted with water (20 mL), and extracted with *n*-pentane (3 x 50 mL) and once with *n*-pentane/diethyl ether (1:1, 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The excess dimethylmalonate was removed by a short path distillaton using Kugelrohr apparatus (2 mm/Hg, 68 °C) to give diester **157** (5.1 g, 70%) as a yellow liquid; R_f 0.32 (3:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2929, 2856, 1743, 1459; δ_H (360 MHz; $CDCl_3$) 1.25-1.30 (2H, m, 4-H), 1.52-1.60 (2H, m, 5-H), 1.84-1.88 (2H, m, 3-H), 2.35 (2H, t, J= 7.5 Hz, 6-H), 3.29 (1H, t, J= 7.6 Hz, 2-H), 3.66 (6H, s, 7-H), 6.18 (1H, dd, J= 1.6 and 0.9 Hz, 4'-H), 7.13 (1H, dt, J= 1.6 and 0.9 Hz, 2'-H), 7.27 (1H, t, J= 1.6 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.7 (t, C), 27.2 (t, C), 29.0 (t, C), 29.9 (t, C), 52.0 (d, 2-C), 52.9 (q, 7-C), 111.3 (d, 4'-C), 125.1 (s, 3'-C), 139.2 (d, 2'-C), 143.1 (d, 5'-C), 170.3 (s, 1-C); *m/z* (EI) 254 (M^+; 61.6%), 191 (33.9), 135 (39), 81 (100); HRMS calcd for $C_{13}H_{18}O_5$ 254.1154, found 254.1125.

6-(Furan-3'-yl)-hexanoic acid methyl ester (158)



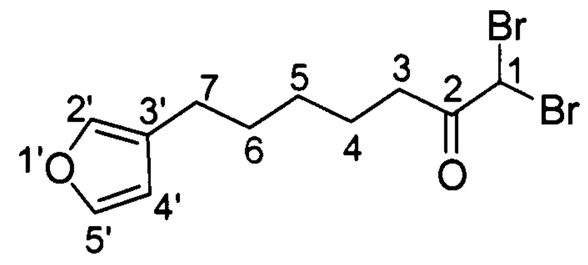
A mixture of diester **157** (3.10 g, 12.3 mmol), DMSO (13 mL), NaCl (400 mg, 15.3 mmol) and distilled water (800 g, 45.5 mmol) were heated at 170 °C for 3h. After cooling, the reaction mixture was poured into cold water (20 mL), followed by extraction with diethyl ether/hexane (1:1, 3 x 20 ml). The organic layers were washed with brine (20 mL) and dried over ($MgSO_4$). Concentration of the organic solvent in vacuo gave a residue that was purified by column chromatography (3:1 petroleum ether/diethyl ether) to afford desired ester **158** (2.2 g, 90%) as a colourless oil; R_f 0.56 (3:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2930, 2858, 1804, 1739; δ_H (360 MHz; $CDCl_3$) 1.30-1.35 (2H, m, 4H), 1.60-1.64 (4H, m, 3,5-H), 2.33 (2H, t, J = 7.5 Hz, 2-H), 2.43 (2H, t, J = 7.5 Hz, 6-H), 3.68 (3H, s, 7-H), 6.27 (1H, dd, J = 1.6 and 0.9 Hz, 4'-H), 7.22 (1H, dt, J = 1.6 and 0.9 Hz, 2'-H), 7.36 (1H, t, J = 1.6 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 25.02 (t, C), 29.1 (t, C), 30.0 (t, C), 34.4 (t, 2-C), 51.1 (q, 7-C), 111.4 (d, 4'-C), 125.4 (s, 3'-C), 139.2 (d, 2'-C), 143.1 (d, 5'-C), 175.6 (s, 1-C); *m/z* (EI) 196 (M^+; 51.2%), 165 (22.5), 95 (50.1), 82 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1103.

1,1-Dichloro-7-(furan-3'-yl)-heptan-2-one (160)



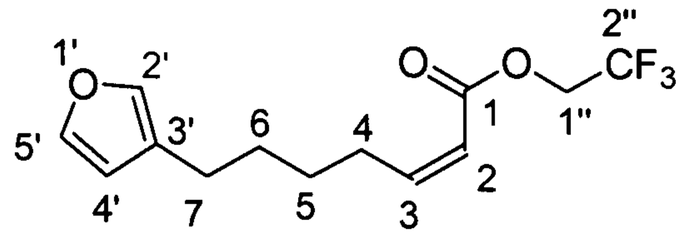
To a stirred solution of DCM (1.80 g, 21.4 mmol) and ester **158** (2.10 g, 10.7 mmol) in THF (22 mL), was added a solution of lithium dicyclohexylamide prepared by [addition of n-BuLi (8.6 ml, 2.5 M, 21.4 mmol) to dicyclohexylamine (3.9 g, 21.4 mmol) in THF (22 mL) at -78 °C] over a period of 10 min at -78 °C. The mixture was stirred for 20 min at this temperature and then hydrolyzed with aqueous HCl (6 M, 11 mL). The solid precipitate was filtered by suction and the filtrate extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$. The solvent was removed in vacuo to give a residue that was purified by column chromatography (10% ether in 60 80 petroleum ether) to give dichloroketone **160** (1.69 g, 63%) pale yellow oil; R_f 0.57 (3:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2932, 2859, 1735, 781; δ_H (360 MHz; $CDCl_3$) 1.30-1.37 (2H, m, 5-H), 1.50-1.55 (2H, m, 4-H), 1.61-1.66 (2H, m, 6-H), 2.36 (2H, t, 3-H), 2.75 (2H, t, 7-H), 5.73 (1H, s, 1-H), 6.19 (1H, dd, J= 1.8 and 0.8 Hz, 4'-H), 7.14 (1H, dt, J= 1.8 and 0.8 Hz, 2'-H), 7.28 (1H, t, J= 1.8 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 23.91 (t, C), 24.9 (t, C), 28.9 (t, C), 30.0 (t, C), 35.2 (t, 3-C), 70.3 (d, 1-C), 111.3 (d, 4'-C), 125.3 (s, 3'-C) 139.2 (d, 2'-C), 143.1 (d, 5'-C), 197.7 (s, 2-C); *m/z* (EI) 248 (M^+; 29%), 165 (60.9), 95 (20), 82 (100); HRMS calcd for $C_{11}H_{14}O_2Cl_2$ 248.0348, found 248.0345.

1,1-Dibromo-7-(furan-3'-yl)-heptane-2-one (161)

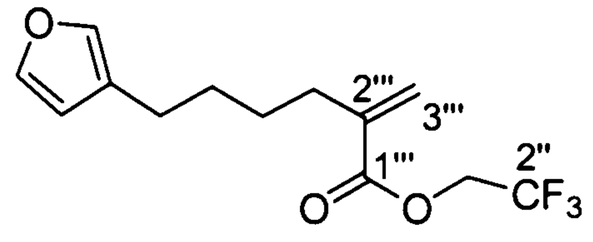


To a solution of ester **158** (500 mg, 2.55 mmol) and dibromomethane (880 mg, 5.10 mmol) in THF (5.2 mL) was added a freshly prepared solution of *n*-BuLi (2.7 mL, 2.5 M, 5.1 mmol) and diisopropylamine (720 μL, 5.10 mmol) in THF (5.2 mL) at -78 °C The mixture was stirred at this temperature for 20 min and then hydrolysed with HCl (6 M, 2.6 mL). The mixture was filtered by suction and the filtrate extracted with diethyl ether (3 x 10 mL). The combined ethereal layer was dried over $MgSO_4$ and the organic solvent removed in vacuo. The crude reaction was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to afford dibromoketone **161** (540 mg, 63%) as an oil; R_f 0.50 (4:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2930, 2856, 1718, 778; δ_H (360 MHz; $CDCl_3$) 1.32-1.40 (2H, m, 5-H), 1.50-1.58 (2H, m, 4-H), 1.62-1.66 (2H, m, 6-H), 2.35 (2H, t, J = 7.5 Hz, 3-H), 2.86 (2H, t, J= 7.3 Hz, 7-H), 5.71(1H, s, 1-H), 6.19 (1H, dd, J= 1.7 and 0.8 Hz, 4'-H), 7.14 (1H, dt, J= 1.7 and 0.8 Hz, 2'-H), 7.27 (1H, t, J= 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.5 (t, C), 24.7 (t, C), 29.3 (t, C), 30.3 (t, C), 35.2 (t, 3-C), 43.3 (d, 1-C), 111.4(d, 4'-C), 125.3 (s, 3'-C), 139.2 (d, 2'-C), 143.1 (d, 5'-C), 197.3 (s, 2-C); *m/z* (EI) 338 (M^+; 12.7%), 165 (57.1), 121 (12), 81 (100); HRMS calcd for $C_{11}H_{14}O_2Br_2Na^+$ 360.9232, found 360.9218.

(*Z*)-7-(Furan-3-yl)-hept-2-enoic acid 2'',2'',2''-trifluoro-ethyl ester (162) and 6-(Furan-3'-yl)-2'''-methylenehexanoic acid 2'',2'',2''-trifluoro-ethyl ester (163)



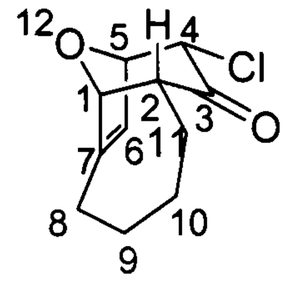
162



163

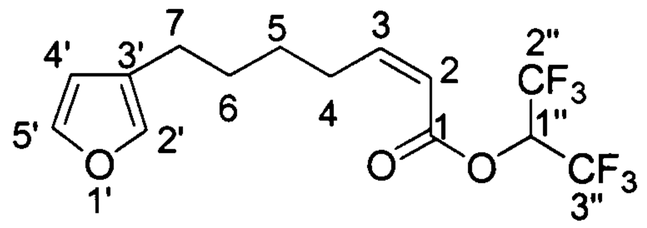
To a solution of dichloroketone **160** (50.0 mg, 200 μmol) in 1,1,1-trifluoroethanol (250 μL, 0.8 M) was added triethylamine (60 μL, 0.44 mmol) at room temperature. The reaction was heated at 50 °C (oil bath) for 24h before quenching with water (3 mL) and extracting with DCM (3 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a residue that was purified by column chromatography (5:1 hexane/ethyl acetate) to give an inseparable mixture of **162** and **163** (31.3 mg, 57%) in a 4:1 ratio; R_f 0.68 (5:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2933, 1734, 1636; δ_H (360 MHz; $CDCl_3$) 1.43-1.50 (4H, m, 5,6-H), 2.36 (2H, t, J= 7.3 Hz, 7-H), 2.60-2.65 (2H, m, 4-H), 4.42 (2H, q, J= 8.2 Hz, 1''-H), 5.59 (2H, d, J= 1.1 Hz, 3'''-H), 5.77 (1H, d, J= 11.5 Hz, 2-H), 6.19 (1H, dd, J= 1.6 and 0.7 Hz, 4'-H), 6.27-6.33 (1H, m, 3- H), 7.13 (1H, dt, J= 1.6 and 0.7 Hz, 2'-H), 7.27 (1H, t, J= 1.6 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.1 (t), 28.0 (t), 28.7 (t), 29.4 (t), 59.7 (q, 1''-C), 110.7 (d, 4'-C), 117.6 (d, 2-C) 124.6 (s, 3'-C), 128.6 (t, 3'''-C), 138.5 (d, 2'-C), 138.8 (s, 2'''-C), 142.3 (d, 5'-C), 153.3 (s, 2''-C), 164.0 (s, 1-C), 165.1 (s, 1'''C); *m/z* (EI) 276 (M^+; 100%), 248 (18.1), 149 (77), 82 (99); HRMS calcd for $C_{13}H_{15}O_3F_3$ 276.0973, found 276.0975.

4-(*endo*)-Chloro-12-oxa-tricyclo[7.2.1.$0^{1,2}$]dodec-6(7)en-3-one (164)



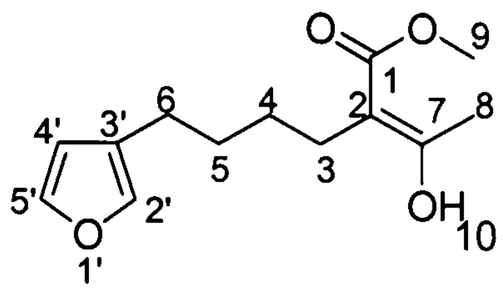
A solution of $NaOCH(CF_3)_2$ (0.5 mL, 0.8 M) in $(CF_3)_2CHOH$ (0.5 mL) was added dropwise to dichloroketone **160** (101 mg, 410 μmol) over a period of 1 h at room temperature. The resulting mixture was stirred at room temperature for 5 days and then quenched with water (10 mL). The aqueous layer was extracted twice with diethyl ether (20 mL) and DCM (20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography (10:1 hexane/ethyl acetate) to give chlorinated ketone **164** (10.5 mg, 12 %) as a pale yellow oil; R_f 0.42 (3:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2936, 1725, 1195; δ_H (360 MHz; $CDCl_3$) 1.22-1.30 (4H, m, 9,10-H), 1.71-1.74 (2H, m, 11-H), 2.41 (2H, t, J= 2.8 Hz, 8-H), 3.00-3.09 (1H, m, 2-H), 4.51 (1H, d, J= 4.4 Hz, 4-H), 4.84 (1H, d, J= 4.4 Hz, 1-H), 4.93-4.98 (1H, m, 5-H), 5.85 (1H, d, J = 1.1 Hz, 6-H); δ_C (90 MHz, $CDCl_3$) 23.7 (t), 26.4 (t), 26.8 (t), 27.0 (t), 56.6 (d, 2-C), 64.2 (d, 4-C), 83.0 (d), 83.5 (d), 124.1 (d, 6-C), 150.7 (s, 7-C), 199.8 (s, 3-C); *m/z* (EI) 212 (M^+; 18%), 178 (15), 177 (100), 107 (41); HRMS calcd for $C_{11}H_{13}O_2{}^{35}ClNa$ (M + Na^+) 235.0496, found 235.0494.

(*Z*)-7-(Furan-3'-yl)-hept-2-enoic acid 2'',2'',2''-trifluoro-1''-trifluoromethyl ethyl ester (165)



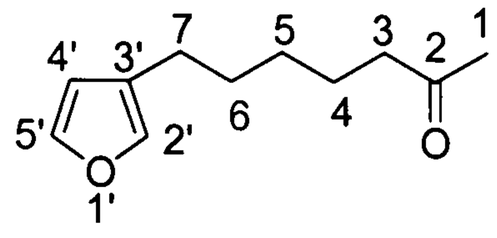
Triethylamine (200 μL, 1.41 mmol) was added dropwise to a solution of dibromoketone **161** (216 mg, 0.64 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (0.8 mL) at room temperature. The reaction was monitored (by TLC) over 7 days by which time there was complete disappearance of starting material. The mixture was quenched with water (5 mL) and the aqueous layer extracted with diethyl ether (10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (7:1 hexane/ethyl acetate) to give first **165** (141 mg, 65%), followed by trace amounts of bromide **166**. Analytical data for **165**: R_f 0.57 (6:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2934, 2862, 1760; δ_H (360 MHz; $CDCl_3$) 1.45-1.50 (4H, m, 5,6-H), 2.37 (2H, t, J = 7.3 Hz, 7-H), 2.61-2.65 (2H, m, 4-H), 5.72-5.80 (1H, septet, J = 5.9 Hz, 1''-H), 5.84 (1H, t, J = 11.4 Hz, 2-H), 6.18 (1H, dd, J = 1.8 and 0.9 Hz, 4'-H), 6.45 (1H, dt, J = 11.4 and 5.6 Hz, 3-H), 7.13 (1H, dt, J = 1.8 and 0.9 Hz, 2'-H), 7.27 (1H, t, J = 1.8 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 24.8 (t), 28.6 (t), 29.7 (t), 29.9 (t), 66.3 (d, 1''-C), 111.3 (d, 4'-C), 116.8 (d, 2-C), 125.1 (s, 3'-C), 139.2 (d, 2'-C), 143.1 (d, 5'-C), 156.8 (d, 3-C), 162.6 (s, 1-C); *m/z* (EI) 344 (M^+; 45%), 276 (13), 149 (30), 89 (100); HRMS calcd for $C_{13}H_{15}O_3F_3$ 344.0847, found 344.0848.

2-Acetyl-6-(furan-3'-yl)-hexanoic acid methyl ester (175a)



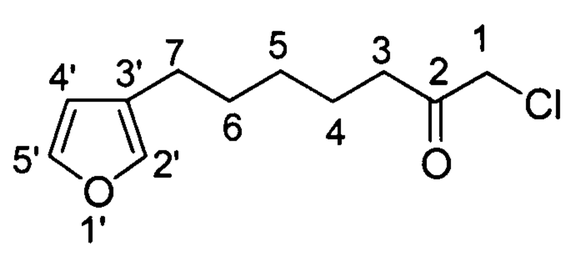
To a solution of NaH (1.30 g, 54.2 mmol) in DMF (39 mL) and THF (100 mL) was added methyl acetoacetate (10 mL, 93.5 mmol) at room temperature. The mixture was stirred for 15 min at room temperature and then bromide **155** (5.4 g, 26.6 mmol) was added. The mixture was reflux for 1.5 h and then cooled and concentrated in vacuo. The organic residue was diluted with water (15 mL) and extracted with diethyl ether (3 x 35 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil. The excess methyl acetoacetate was removed by distillation (2 mm/Hg, 80-95 °C) to afford enol **175a** (5.3 g, 82%) as a pale yellow oil that was used without further purification; R_f 0.42 (4:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2946, 2863, 1706, 1628, 1436, 782; δ_H (360 MHz; $CDCl_3$) 1.72-1.76 (4H, m, 4,5-H), 2.31 (3H, s, 8-H), 2.48 (2H, t, J = 7.2 Hz, 6-H), 3.68 (3H, s, 9-H), 3.77 (2H, t, J = 6.2 Hz, 3-H), 5.01 (1H, s, 10-H), 6.28 (1H, dd, J = 1.6 and 0.8 Hz, 4'-H), 7.28 (1H, dt, J = 1.6 and 0.8 Hz, 2'-H), 7.37 (1H, t, J = 1.6 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 19.5 (q, 8-C), 24.8 (t, 3-C), 26.8 (t, 6-C), 28.6 (t, 4-C), 32.1 (t, 5-C), 51.1 (q, 9-C), 111.2 (d, 4'-C), 125.0 (s, 2-C), 139.3 (d, 2'-C), 143.1 (d, 5'-C), 168 (s, 1-C), 173 (s, 7-C); m/z (EI) 238 (M^+; 20.4%), 220 (100), 161 (33), 82 (100); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1209.

7-(Furan-3'-yl)-heptan-2-one (176)

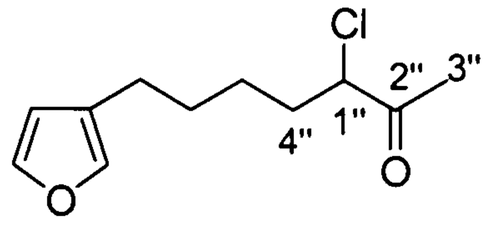


A mixture of enol **175a** (5.30 g, 22.3 mmol), DMSO (20 mL), NaCl (1.60 g, 27.8 mmol), and distilled water (1.50 g, 83.3 mmol) was heated at 170 °C (oil bath) for 3 h and then poured into cold water (10 mL). The reaction mixture was extracted with diethyl ether/hexane (1:1, 3 x 40 mL). The combined organic extracts was washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to give ketone **176** (2.2 g, 60%) as a pale yellow oil; R_f 0.58 (4:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2933, 2860, 1710, 1498; δ_H (360 MHz; $CDCl_3$) 1.32-1.37 (2H, m, 5-H), 1.57-1.60 (4H, m, 4,6-H), 2.14 (3H, s, 1-H), 2.74-2.88 (4H, m, 3,7-H), 6.27 (1H, dd, J = 1.7 and 0.8 Hz, 4'-H), 7.21 (1H, dt, J = 1.7 and 0.8 Hz, 2'-H), 7.35 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 25.5 (t, C), 26.5 (t, C), 30.7 (t, C), 31.7 (t, C), 31.8 (q, 1-C), 45.6 (t, C), 112.9 (d, 4'-C), 126.9 (s, 3'-C), 140.7 (d, 2'-C), 144.6 (d, 5'-C), 211.1 (s, 2-C); m/z (EI) 180 (M^+; 2.5%), 178 (52), 95 (33), 82 (100); HRMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1146.

1-Chloro-7-(furan-3'-yl)-heptan-2-one (177) and 3-Chloro-7-(furan-3'-yl)-heptan-2-one (178)



177



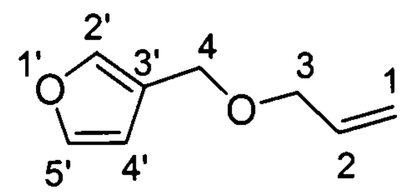
178

From compound (176). *n*-BuLi (hexane, 7.50 mL, 1.2M, 9.01 mmol) was added to a solution of diisopropylamine (1.30 mL, 8.70 mmol) in THF (64 mL) at 0 °C. The solution was stirred for 20 min at this temperature before **176** (640 mg, 3.60 mmol) in THF (6.5 mL) was added at -78 °C. The mixture was stirred for 30 min before a solution of NCS (1.20 g, 9.00 mmol) in THF (20 mL) wad added. The reaction mixture was allowed to warm to room temperature before quenching with aqueous NH_4Cl (15 mL). The reaction was extracted with diethyl ether (3 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue that was purified by column chromatography (10% ethyl acetate in 60-80 petroleum ether) to give an inseparably mixture of **177** and **178** (78 mg, 12%) in a 5:1 ratio.

From compound (158). A solution of diisopropylamine (4.60 mL, 23.0 mmol) in THF (50 mL) was treated with *n*-BuLi (hexane, 14.6 mL, 1.4M, 20.4 mmol) at 0 °C. The solution was stirred for 30 min then cooled to -78 °C before a solution of **158** (1.01 g, 5.10 mmol) and CH_2ICl (1.50 mL, 20.4 mmol) in THF (28 mL) was added over 20 min. The reaction mixture was stirred for 10 min and then warmed to -75 °C before acetic acid (7.7 mL) in THF (51 mL) was added while maintaining the reaction temperature below -65 °C. The reaction mixture was stirred for a further 10 min at -75 °C before quenching with brine (5 mL). The reaction was extracted with ethyl acetate

(3 x 20 mL) and the combined organic layer washed with aqueous $NaHSO_4$ (15 mL), 5% $NaHCO_3$ (15 mL) solution and brine. The reaction organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (10% ethyl acetate in 60-80 petroleum ether) to give a mixture of compounds **177** and **178** (300 mg, 27%) in a 5:1 ratio; R_f 0.35 (10% ethyl acetate in 60-80 petroleum ether); υ_{max} (neat)/cm^{-1} 2935, 1718, 778; δ_H (360 MHz; $CDCl_3$) 1.33-1.38 (2H, m, 5-H), 1.58-1.63 (4H, m, 4,5-H), 1.91-1.95 (2H, m, 4''-H), 2.33 (3H, s, 3''-H), 2.43 (2H, t, ^3J = 7.4 Hz, 7-H), 2.61 (2H, t, J = 7.4 Hz, 3-H), 4.08 (2H, s, 1-H), 4.19 (1H, dd, J = 8.5 and 5.5 Hz, 1''-H), 6.27 (1H, dd, J = 1.8 and 0.9 Hz, 4'-H), 7.22 (1H, dt, J = 1.8 and 0.9 Hz, 5'-H), 7.35 (1H, t, J = 1.8 Hz, 2'-H); δ_C (90 MHz, $CDCl_3$) 23.7 (t, C), 24.8 (t, C), 26.4 (q, 3''-C), 29.0 (t, C), 30.1 (t, C), 33.9 (t, 4''-C), 40.0 (t, 3-C), 48.6 (t, 1-C), 64.5 (d, 1''-C), 111.3 (d, 4'-C), 125.3 (s, 3'-C), 139.2 (d, 2'-C), 143.2 (d, 5'-C), 203.1 (s, 2-C), 203.8 (s, 2''-C); *m/z* (EI) 214 (M^+; 25.0%), 165 (9), 82 (100); HRMS calcd for $C_{11}H_{15}O_2{}^{35}ClNa^+$ 237.0235, found 237.0237.

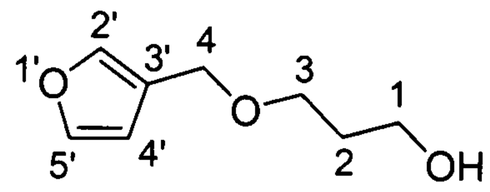
3'-(Allyloxymethyl)-furan (179)



To a freshly distilled solution of alcohol **136** (3.80 g, 38.8 mmol) in dry DMF (90 mL) was added NaH (2.30 g, 97.0 mmol). The mixture was stirred at room temperature for 30 min and then allylchloride (8 mL, 93.1 mmol) was added dropwise. The reaction mixture was stirred for a further 3 h at room temperature and then brine (30 mL) was cautiously added. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and

the combined organic layer was washed with saturated aqueous NH_4Cl (20 mL), dried (MgSO4) and concentrated in vacuo. The crude reaction was purified by distillation using kugelrohr apparatus (2mm / Hg, 40-60 °C) to afford compound **179** (4.1 g, 77%) as a colourless liquid; R_f 0.44 (2:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2854, 1642, 1502; δ_H (360 MHz; $CDCl_3$) 3.91-3.94 (2H, m, 3-H), 4.32 (2H, s, 4-H), 5.25-5.28 (2H, m, 1-H), 5.94-5.96 (1H, m, 2-H), 6.45 (1H, dd, J = 1.7 and 0.9 Hz, 4'-H), 7.31 (1H, dt, J = 1.7 and 0.9 Hz, 2'-H), 7.43 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 63.7 (t, 3-C), 71.3 (t, 4-C), 110.8 (d, 2-C), 117.6 (t, 1-C), 122.6 (s, 3'-C), 135.1 (d, 4'-C), 141.0 (d, 2'-C), 143.7 (d, 5'-C); *m/z* (EI) 138 (M^+; 14.3%), 108 (5.5), 95 (13.4), 81 (100), 53 (29.7).

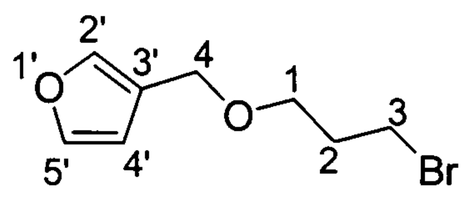
3-(Furan-3'-yl-methoxy)-propan-1-ol (180)



To a solution of borane-dimethyl sulfide (4.14 ml, 46.7 mmol) and 2-methyl-2-butene (46 mL, 93.6 mmol) in THF (36 mL) was added olefin **179** (2.15 g, 15.6 mmol). The mixture was stirred for 1h at room temperature and then quenched carefully with NaOH (3M, 40 ml) and 27% H_2O_2 (16 mL). The mixture was stirred for a further 1h and then diluted with water (15 mL) and extracted with diethyl ether (3 x 50ml). The ethereal layer was dried over $MgSO_4$ and the solvent removed in vacuo. The crude reaction was purified by column chromatography (3:2 60-80 petroleum ether/diethyl ether) to afford alcohol **180** (1.57 g, 65%); R_f 0.25 (3:2 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 3400 (*br)*, 2940, 2868, 1502; δ_H (360 MHz; $CDCl_3$) 1.82-1.86

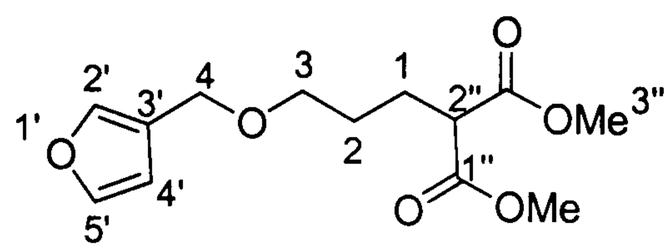
(2H, m, 2-H), 2.32 (1H, s, O-H), 3.65 (2H, t, J = 5.8 Hz, 1-H), 3.69-3.73 (2H, m, 3-H), 4.40 (2H, s, 4-H), 6.42 (1H, dd, J = 1.7 and 0.7 Hz, 4'-H), 7.32 (1H, dt, J = 1.7 and 0.7 Hz, 2'-H), 7.43 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 32.4 (t, 2-C), 62.3 (t, 1-C), 64.8 (t, 3-C), 69.5 (t, 4-C), 110.6 (d, 4'-C), 122.5 (s, 3'-C), 141.0 (d, 2'-C), 143.8 (d, 5'-C); *m/z* (EI) 156 (M^+; 3.9%), 97 (58.3), 81 (100), 53 (17.7); HRMS calcd for $C_8H_{12}O_3$ 156.0780, found 156.0786.

3'-(3-Bromopropoxymethyl)-furan (181)



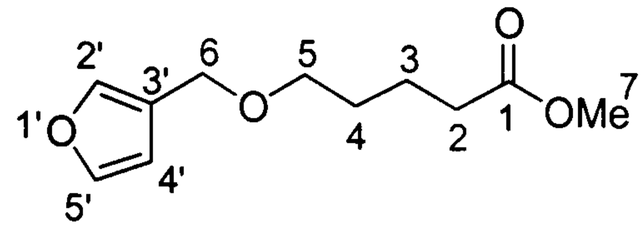
To a solution of alcohol **180** (3.90 g, 25.0 mmol) and CBr_4 (10.0 g, 30.0 mmol) in dry DCM (33 mL), was added triphenyl phosphine (10.5 g, 40.0 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h and then the solvent was removed in vacuo to give a residue that was purified by column chromatography (4:1 60-80 petroleum/ether) to give bromide **181** (4.10 g, 75%) as a colourless liquid; R_f 0.55 (4:1 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2864, 1598, 1500, 732; δ_H (360 MHz; $CDCl_3$) 2.14-2.20 (2H, tt, J = 6.5 and 5.9 Hz, 2-H), 3.53 (2H, t, J = 6.5 Hz, 3-H), 3.69 (2H, t, J = 5.9 Hz, 1-H), 4.41 (2H, s, 4-H), 6.57 (1H, dd, J = 1.6 and 0.6 Hz, 4'-H), 7.33 (1H, dt, J = 1.6 and 0.6 Hz, 2'-H), 7.45 (1H, t, dd, J = 1.6 Hz); δ_C (90 MHz, $CDCl_3$) 31.1 (t, 2-C), 33.2 (t, 3-C), 64.7 (t, 1-C), 67.8 (t, 4-C), 110.7 (d, 4'-C), 122.6 (s, 3'-C), 141.0 (d, 2'-C), 143.8 (d, 5'-C); *m/z* (EI) 219 (M^+; 10%), 121 (51.6), 97 (5.6), 81 (100), 65 (26.7); calcd for $C_8H_{12}O_2{}^{79}BrNa^+$ 242.1305, found 242.1303.

2''-[3-(Furan-3'-ylmethoxy)-propyl]malonic acid dimethyl ester (182)



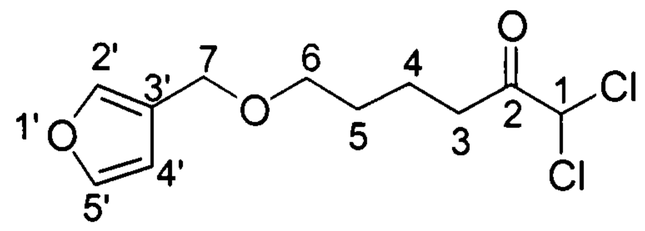
To a solution of NaH (1.10 g, 37.4 mmol) in DMF (27 mL) and THF (54 mL) was added dimethyl malonate (10 ml, 93.5 mmol) at 0 °C. The mixture was stirred for 15 min at room temperature and then bromide **181** (4.10 g, 18.7 mmol) was added. The mixture was brought to reflux for 1.5 h and the THF removed. The residue was diluted with water (15 mL) and extracted with diethyl ether (3 x 35 mL). The combined organic layers were dried and concentrated in vacuo. The excess dimethyl malonate was removed by short-path distillation using a Kugelröhr apparatus (2 mm/Hg, 68 °C) to afford compound **157** (4.17 g, 82%) as a liquid; R_f 0.43 (1:1 *n*-pentane/diethyl ether); υ_{max} (neat)/cm^{-1} 2930, 2856, 1745, 1475; δ_H (360 MHz; $CDCl_3$) 1.60-1.68 (2H, m, 1,2-H), 2.26 (2H, t, J = 7.3 Hz, 2''-H), 3.38 (2H, t, J = 6.2 Hz, 3-H), 3.65 (3H, s, 3''-H), 4.28 (2H, s, 4-H), 6.33 (1H, dd, J = 1.7 and 0.7 Hz, 4'-H), 7.28 (1H, dt, J = 1.7 and 0.7 Hz, 2'-H), 7.32 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 30.6 (t, 1-C), 34.1 (t, 2-C), 51.8 (d, 2''-C), 52.9 (q, 3''-C), 64.4 (t, 3-C), 69.9 (t, 4-C), 110.7 (d, 4'-C), 122.8 (s, 3'-C), 140.9 (d, 2'-C), 143.6 (d, 5'-C), 173.7 (s, 1''-C); *m/z* (EI) 270 (M^+; 2.7%), 187 (100), 139 (8.0), 111 (10.3); calcd for $C_{13}H_{18}O_6Na^+$ 293.0211, found 293.0210.

5-(furan-3'-ylmethoxy)-pentanoic acid methyl ester (183)



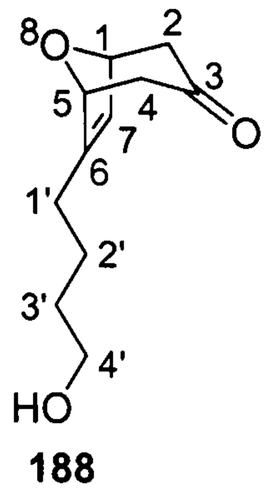
A mixture of diester **182** (4.10 g, 15.5 mmol), DMSO (15 mL), NaCl (1.10 g, 19.0 mmol), and distilled water (1.10 g, 58.7 mmol) was heated at 170 °C for 3 h. The mixture was poured into cold water (10 mL) and extracted with diethyl ether/hexane (1:1, 3 x 35 mL). The organic extracts were washed with brine (30 mL), dried over MgSO4 and the organic solvent removed in vacuo to give a residue that was purified by column chromatography using (4:1 60-80 petroleum ether/diethyl ether) to give compound **183** (2.0 g, 65%) as a pale yellow liquid; R_f 0.52 (4:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2928, 2856, 1730, 1510; δ_H (360 MHz; $CDCl_3$) 1.66-1.69 (4H, m, 3,4-H), 2.35 (2H, t, J = 7.3 Hz, 2-H), 3.47 (2H, t, J = 6.2 Hz, 5-H), 3.68 (3H, s, 7-H), 4.37 (2H, s, 6-H), 6.44 (1H, dt, J = 1.9 and 0.8 Hz, 4'-H), 7.38 (1H, dt, J = 1.9 and 0.8 Hz, 2'-H), 7.41 (1H, t, J = 1.9 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 21.14 (t, 3-C), 28.5 (t, 4-C), 33.2 (t, 2-C), 50.9 (q, 7-C), 63.5 (t, 5-C), 69.0 (t, 6-C), 109.7 (d, 4'-C), 121.8 (s, 3'-C), 139.9 (d, 2'-C), 142.7 (d, 5'-C), 173.4 (s, -1C); *m/z* (EI) 212 (M^+; 11.1%), 171 (8.0), 111 (6.8), 81 (100); calcd for $C_{11}H_{16}O_4Na^+$ 235.3014, found 235.3008.

1,1-Dichloro-6-(furan-3'-ylmethoxy)-hexan-2-one (184)

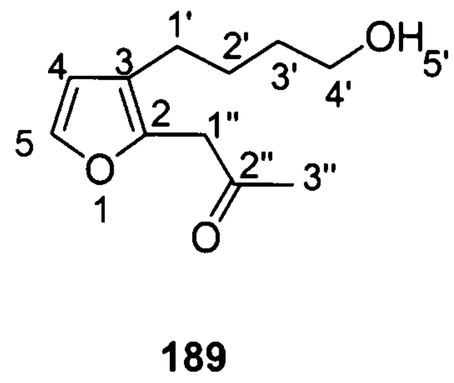


To a stirred solution of DCM (700 μL, 11.0 mmol) and ester **183** (1.10 g, 5.20 mmol) in THF (11 mL), was added a solution of *n*-BuLi (5.50 mL, 2.5 M, 11.0 mmol) and dicyclohexylamine (2.20 mL, 11.0 mmol) in THF (11 mL) at –78 °C. The reaction mixture was stirred for 20 min at this temperature and then hydrolysed using HCl (6M, 5.2 mL). The solid precipitate was filtered off and the filtrate extracted with diethyl ether (3 x 30 mL). The combined ethereal extracts were dried over $MgSO_4$ and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to give dichloroketone **184** (1.0 g, 74%) as a yellow liquid; R_f 0.55 (3:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2930, 2856, 1725, 730 δ_H (360 MHz; $CDCl_3$) 1.72-1.78 (4H, m, 4,5-H), 2.87 (2H, t, J = 7.1 Hz, 3-H), 3.48 (2H, t, J = 6.2 Hz, 6-H), 4.38 (2H, s, 7-H), 5.82 (1H, s, 1-H), 6.43 (1H, dt, J = 1.7 and 0.8 Hz, 4'-H), 7.38 (1H, dt, J = 1.7 and 0.8 Hz, 2'-H), 7.40 (1H, t, J = 1.7 Hz, 5'-H); δ_C (90 MHz, $CDCl_3$) 21.1 (t, 5-C), 29.2 (t, 4-C), 35.0 (t, 3-C), 64.5 (t, 6-C), 70.0 (t, 7-C), 70.3 (d, 1-C), 110.7 (d, 4'-C), 122.7 (s, 3'-C), 140.1 (d, 2'-C), 143.8 (d, 5'-C), 197.5 (s, -2C); *m/z* (EI) 264 (M^+; 2.5%), 132 (11.8), 81 (100), 53 (9.1); calcd for $C_{11}H_{14}O_3{}^{35}Cl_2Na^+$ 287.5128, found 287.5131.

6-(4'-Hydroxy-butyl)-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (188) and 1''-[3-(4'-Hydroxy-butyl)-furan-2-yl]-propan-2''-one (189)



188



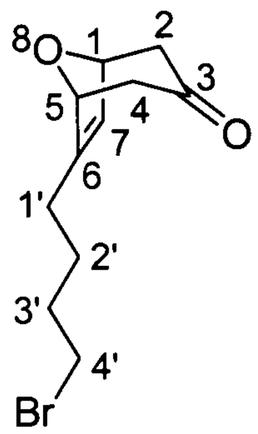
189

A solution of $NaOCH_2CF_3$ (10.7 mL, 21.4 mmol) in CF_3CH_2OH (10.7 mL) and 1,3,3-trichloroacetone (2.30 mL, 2.40 mmol) were added separately via syringe to alcohol **139** (1.50 g, 10.7 mmol) over 1 h at 0 °C. The reaction was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched with water (15 mL) and extracted with diethyl ether (3 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a crude product that was dissolved in methanol (10 mL) and added to a solution of Zn (14.8 g, 227 mmol) and Cu(I)Br (8.70 g, 60.6 mmol) in methanol (130 mL). The mixture was stirred at room temperature for 2 days before filtering through 10 g of Celite and the filtrate concentrated to give a residue the was dissolved in a 5% solution of HCl. The aqueous layer was extracted with diethyl ether (3 x 40 mL) and once with ethyl acetate (45 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to a residue that was purified by column chromatography (3:1 60-80 petroleum ether/ethyl acetate) to give first compound **189** (78 mg, 4%) as a pale yellow oil, followed by **188** (807 mg, 54% over two steps) as a colourless oil. Analytical data for **188**: R_f 0.23 (3:1 ethyl acetate/60-80 petroleum ether); υ_{max} (neat) 3430 (*br*), 2940, 1708 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.49-1.53 (4H, m, 2',3'-H), 1.82 (1H, br, OH), 2.08 (2H, br, 1'-H), 2.22-2.30 (2H, m, 2,4-H), 2.59-

2.64 (2H, m, 2,4-H), 3.57 (2H, t, J = 5.4 Hz, 4'-H), 4.72 (1H, d, J = 4.9 Hz, 5-H), 4.92 (1-H, m, 1-H), 5.76 (1H, ap, J = 1.7 Hz, 7-H); δ_C (90 MHz, $CDCl_3$) 23.9 (t), 27.3 (t), 32.6 (t), 46.5 (t), 46.6 (t), 62.9 (t), 78.0 (d), 80.0 (d), 126.1 (d, 7-C), 148.0 (s, 6-C), 206.4 (s, 3-C); *m/z* (EI) 196 (M^+; 97.3%), 178 (43), 153 (92), 95 (100); HRMS calcd for $C_{11}H_{16}O_3Na$ 219.0992, found 219.0989.

Analytical data for **189**: R_f 0.42 (3:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 3540 (*br*), 2952, 1765; δ_H (360 MHz; $CDCl_3$) 1.56-1.62 (5H, m, 2',3',5'-H), 2.15 (3H, s, 3''-H), 2.40 (2H, t, J = 7.1 Hz, 1'-H), 3.65 (2H, s, 1''-H), 3.64-3.70 (2H, m, 4'-H), 6.28 (1H, d, J = 1.8 Hz, 4-H), 7.32 (1H, d, J = 1.8 Hz, 5-H); δ_C (90 MHz, $CDCl_3$) 24.8 (t), 26.8 (t), 29.6 (q, 3''-C), 32.5 (t), 42.0 (t), 63.0 (t, 1''-C), 112.1 (d, 4-C), 122.3 (s, 3-C), 141.9 (d, 5-C), 144.0 (s, 2-C), 205.3 (s, 2''-C); *m/z* (EI) 196 (M^+; 100%), 179 (61), 151 (53); HRMS calcd for $C_{11}H_{16}O_3Na^+$ 219.0992, found 219.0973.

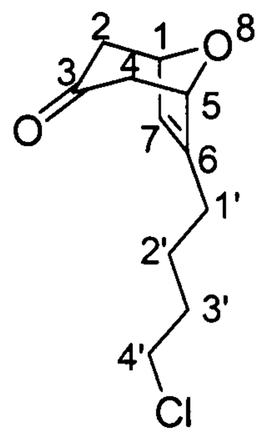
6-(4'-Bromo-butyl)-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (190)



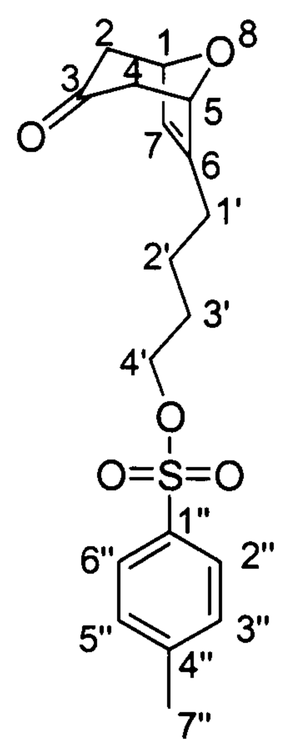
To a solution of alcohol **188** (1.01 g, 5.10 mmol) and carbon tetrabromide (2.10 g, 6.30 mmol) in DCM (30 mL) was added portionwise triphenylphosphine (2.10 g, 8.01 mmol) at 0 °C. The mixture was stirred for 2 h while warming to room temperature.

The reaction was quenched with water (10 mL), followed by extraction with DCM (3 x 20 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. Concentration of the organic layer in vacuo gave a residue that was purified by column chromatography (2:1 60-80 petroleum ether/ethyl acetate) to give compound **190** (940 mg, 71%) as a colorless oil; R_f 0.45 (3:2 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2949, 1711, 789; δ_H (360 MHz; $CDCl_3$) 1.53-1.64 (2H, m, 2'-H), 1.77-1.85 (2H, m, 3'-H), 2.05-2.13 (2H, m, 1'-H), 2.21-2.33 (2H, m, 2,4- H), 2.63-2.71 (2H, m, 2,4- H), 3.34 (2H, t, J = 6.6 Hz, 4'-H), 4.79 (1H, d, J = 4.9 Hz, 5-H), 5.00 (1H, m, 1-H), 5.85 (1H, ap, J = 1.8 Hz, 7-H); δ_C (90 MHz, $CDCl_3$) 26.09 (t), 26.6 (t), 32.0 (t), 32.5 (t), 33.8 (t), 46.5 (t, 4'-C), 78.0 (d), 79.4 (d), 126.3 (d, 7-C), 148.0 (s, 6-C), 206.1 (s, 3-C); *m/z* (EI) 258 (M^+; 36.7%), 217 (100), 279 (35), 137 (59); HRMS calcd for $C_{11}H_{15}O_2{}^{79}BrNa^+$ 281.0148, found 281.0141

(±)-6-(4'-Chloro-butyl)-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (191) and (±)-Toluene-4'-sulfonic acid-4'-(3-oxo-8-oxa-bicyclo[3.2.1]oct-6-en-6-yl)-butyl ester (192)



191



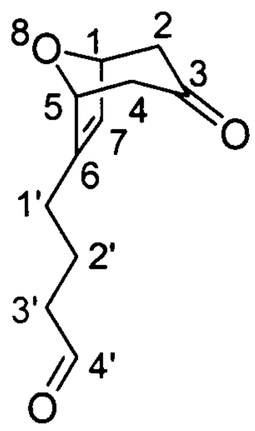
192

To a suspension of alcohol **188** (200.0 mg, 1.02 mmol), 4-DMAP (11.0 mg, 0.09 mmol), and triethylamine (0.63 mL, 4.52 mmol) in DCM (11 mL) was added *p*-toluenesulfonyl chloride (328 mg, 1.72 mmol) in one portion with cooling in an ice-water bath. The reaction was stirred for 4.5 h while warming to room temperature and then diluted with diethyl ether (15 mL). The organic phase was washed with aqueous sodium bicarbonate solution and dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography (2:1 petroleum ether 60-80/ethyl acetate) to give first chloroketone **191** (23%, 50 mg), followed by compound **192** (227 mg, 64%) as a solid. Analytical data for **191**: R_f 0.48 (2:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2948, 1709, 855; δ_H (360 MHz; $CDCl_3$) 1.68-1.73 (2H, m, 2'-H), 1.80-1.84 (2H, m, 3'-H), 2,12-2.18 (2H, m, 1'-H), 2.31-2.39 (2H, m, 2,4-H), 2.70-2.78 (2H, m, 2,4-H), 3.55 (2H, d, J = 6.4 Hz, 4'-H), 4.75 (1H, d, J = 4.9 Hz, 5-H), 4.98-5.18 (1H, m, 1-H), 5.85 (1H, ap, J = 1.7 Hz, 7-H); δ_C (90 MHz, $CDCl_3$) 24.9 (t), 26.7 (t), 32.4 (t, 1'-C), 45.1 (t), 46.5 (t), 66.3 (t, 4'-C), 78.0 (d), 79.5 (d), 126.4 (d,

7-C), 148.0 (s, 6-C), 206.1 (s, 3-C); *m/z* (EI) 214 (M^+; 36%), 171 (100), 81 (46); HRMS calcd for $C_{11}H_{15}O_2{}^{35}ClNa^+$ 214.0755, found 214.0762.

Analytical data for **192**: mp 42-43 °C; R_f 0.33 (2:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2930, 2360, 1700, 1050; δ_H (360 MHz; $CDCl_3$) 1.48-1.54 (4H, m, 2',3'-H), 1.96-2.01 (2H, m, 1'-H), 2.21-2.24 (2H, m, 2,4-H), 2.39 (3H, s, 7''-H), 2.63-2.68 (2H, m, 2,4-H), 3.96 (2H, t, J = 6.1 Hz, 4'-H), 4.67 (1H, d, J = 4.9 Hz, 5-H), 4.88-4.92 (1H, m, 1-H), 5.71 (1H, q, J = 1.8 Hz, 7-H), 7.36 (2H, d, J = 8.1 Hz, 3'',5''-H), 7.30 (2-H, d, J = 8.3 Hz, 2'',6''-H); δ_C (90 MHz, $CDCl_3$) 22.1 (q, 7''-C), 23.6 (t), 26.8 (t), 28.8 (t), 46.5 (t, 4'-C), 70.4 (t), 78.0 (d, 4-C), 79.4 (d), 126.3 (d, 7-C), 128.3 (d), 130.3 (d), 133.4 (s), 145 (s), 147.8 (s), 206.0 (s, 3-C); *m/z* (EI) 350 (M^+; 100%), 178 (22), 135 (67), 121 (18); HRMS calcd for $C_{14}H_{14}O_3F_6S$ 350.1188, found 350.1172.

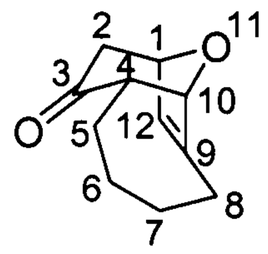
(±)-4'-(3-Oxo-8-oxa-bicyclo[3.2.1]oct-6-en-6-yl)-butyraldehyde (193)



A solution of alcohol **188** (100 mg, 510 μmol) in DCM (10 mL) was treated with Dess-Martin periodinane (109 mg, 260 μmol) at room temperature. The mixture was stirred at room temperature for 18 h then a solution of $Na_2S_2O_3$ (1 M, 10 mL) was added. The mixture was extracted with DCM and the organic layer washed with 5%

aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (2:1 ethyl acetate/60-80 petroleum ether) to give compound **193** (40 mg, 81%) as a yellow oil; R_f 0.29 (2:1 ethyl acetate/60-80 petroleum ether); υ_{max} (neat)/cm^{-1} 2940, 1716, 1650, 1048; δ_H (360 MHz; $CDCl_3$) 1.74-1.94 (2H, m, 2'-H), 2.11-2.22 (2H, m, 1'-H), 2.28-2.40 (2H, m, 2,4-H), 2.49-2.52 (2H, m, 3'-H), 2.71-2.80 (2H, m, 2,4-H), 4.79 (1H, d, J = 4.9 Hz, 5-H), 5.05-5.24 (1H, m, 1-H), 5.86 (1H, ap, J = 1.7 Hz, 7-H), 9.80 (1H, d, J = 1.2 Hz, 4'-H); δ_C (90 MHz, $CDCl_3$) 19.9 (t), 26.7 (t), 43.5 (t), 46.5 (t), 78.0 (d), 79.4 (d), 126.6 (d, 7-C), 147.6 (s, 6-C), 201.9 (d, 4'-C), 206.0 (s, 3-C); *m/z* (EI) 194 (M^+; 100%), 177 (70), 108 (56); HRMS calcd for $C_{11}H_{14}O_3Na^+$ 217.1135, found 217.1131.

(±)-11-Oxa-tricyclo[7.2.1.$0^{4,10}$]dodec-9(12)-en-3-one (195)

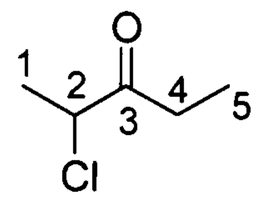


To a stirred solution of KO-*t*-Bu (50 mg, 0.45 mmol) in THF (38 mL) was added a solution of **192** (120 mg, 340 μmol) in THF (110 mL). The mixture was refluxed for 1 h and then a further 1.3 equivalents of KO-*t*-Bu (50 mg, 450 μmol) was added in one portion. The resulting mixture was refluxed for 30 min, by which time the reaction was seen to have gone to completion (by TLC). The reaction was quenched with saturated aqueous NH_4Cl, followed by extraction of the aqueous layer with diethyl ether. The ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to afford the titled compound (47 mg, 80%) as a yellow solid; mp 72-73 °C; R_f 0.42 (3:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2932, 2858, 1704, 1046; δ_H (360 MHz;

$CDCl_3$) 1.10-1.18 (4H, m, 6,7-H), 1.48-1.56 (1H, m, 5-H), 1.68-1.73 (1H, m, 5-H), 2.12-2.18 (1H, m, 2-H), 2.22-2.29 (2H, m, 8-H), 2.56 (1H, d, J = 4.6 Hz, 2-H), 2.60-2.78 (1H, dt, J = 4.4 and 1.6 Hz, 4-H), 4.72 (1H, d, J = 4.4 Hz, 10-H), 4.97 (1H, q, J = 1.6 Hz, 1-H), 5.64 (1H, s (br), 12-H); δ_C (90 MHz, $CDCl_3$) 23.7 (t), 26.1 (t), 26.6 (t), 38.1 (t, 8-C), 46.27 (t, 4-C), 56.2 (d, 4-C), 78.9 (d, 10-C), 82.4 (d, 1-C), 126.9 (d, 12-C), 147.5 (d, 7-C), 207.6 (s, 3-C); *m/z* (EI) 178 (M^+; 100%), 149 (24), 121 (41), 79 (27); HRMS calcd for $C_{11}H_{14}O_2$ 179.1072, found 179.1073.

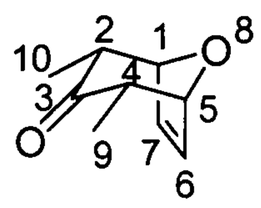
Crystal data for **195**: C_{11} H_{14} O_2, M = 178.22, colourless block, 0.80 × 0.80 × 0.30 mm^3, monoclinic, space group $C2/c$ (No. 15), a = 22.1341(6), b = 7.6802(3), c = 11.0101(3) Å, β = 107.876(2)°, V = 1781.30(10) $Å^3$, Z = 8, D_c = 1.329 g/cm^3, F_{000} = 768, Nonis KappaCCD CCD diffractometer, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, $2\theta_{max}$ = 55.0°, 2933 reflections collected, 1813 unique (R_{int} = 0.0505). The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) respectively. The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs, and to prepare the figures. Final *GooF* = 1.063, *R1* = 0.0397, *wR2* = 0.0971, *R* indices based on 1548 reflections with I >2sigma(I) (refinement on F^2), 119 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.090 mm^{-1}.

2-Chloro-pentan-3-one (242)[125]



To a heated (45 °C) solution of 3-pentanone (69.4 g, 800 mmol) in CCl_4 (200 mL) was added dropwise sulfuryl chloride (71.0 mL, 873 mmol) over 2 h. The resulting mixture was stirred for 18 h at 45 °C and the excess CCl_4 was removed under atmospheric pressure at 85 °C to give essentially pure **242** (86.4 g, 90%) as a yellow oil; υ_{max} (neat)/cm^{-1} 2958, 1712, 805; δ_H (360 MHz; $CDCl_3$) 1.02 (3H, t, J = 7.3 Hz, 5-H), 1.53 (3H, d, J = 7.0 Hz, 1-H), 2.58 (2H, q, J = 14.5 and 7.3 Hz, 4-H), 4.26 (1H, q, J = 13.7 and 7.0 Hz, 2-H); δ_C (90 MHz, $CDCl_3$) 8.2 (q, 5-C), 20.7 (q, 1-C), 32.0 (t, 4-C), 58.7 (d, 2-C), 206.6 (s, 3-C); *m/z* (EI) 120 (M^+; 20%), 91 (89), 63 (100).

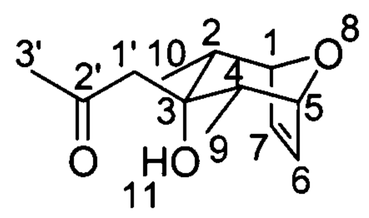
2,4-*endo*,*endo*-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (243)[125]



To a vigorously stirred solution of 2-chloro-penta-3-one (15.0 g, 124.8 mmol) and furan (34.0 g, 499.2 mmol) in water (126 mL) was added triethylamine (13.4 g, 131.0 mmol) at room temperature. The resulting mixture was stirred for 24 h at room temperature and then quenched with aqueous NH_4Cl. The reaction was extracted with DCM and concentrated to give a residue that was re-subjected to the reaction conditions base on 40% of un-reacted starting material (water (70 mL), furan (19.0 g,

279 mmol) and triethylamine (7.5 g, 73.4 mmol)). The solid precipitate was filtered, washed with hexane and the filtrate concentrated and cooled to -20 °C. The solid precipitate was filtered and washed with hexane. This procedure was repeated until no solid was formed at -20 °C. The combined precipitates were dried under vacuum to give the *title compound* (12.3 g, 65%); R_f 0.60 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2958, 1708, 1046; δ_H (360 MHz; $CDCl_3$) 0.97 (6H, d, J = 7.1 Hz, 9,10-H), 2.77-2.81 (2H, m, 2,4-H), 4.86 (2H, d, J = 4.5 Hz, 1,5-H), 6.34 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 10.5 (q, 9,10-C), 50.8 (d, 2,4-C), 83.1 (d, 1,5-C), 133.9 (d, 6,7-C), 209.5 (s, 3-C); *m/z* (EI) 152 (M^+; 45%), 137 (20), 81 (100).

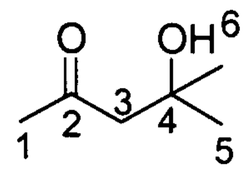
1'-(3-*endo*-Hydroxy-2,4-(*endo*,*endo*)-dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yl)-propan-2'-one (247)



A mixture of ester **256** (110 mg, 410 μmol), DMSO (1.0 mL), LiCl (35.0 mg, 820 μmol) and distilled water (30 mg, 1.6 mmol) were refluxed for 3 h. After cooling, the reaction mixture was poured into cold water (10 mL), followed by extraction with diethyl ether/hexanes (1:1, 3 x 20 mL). The organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (1:1 hexane/ethyl acetate) to give the *title compound* (8 mg, 9%) as a colourless oil; R_f 0.35 (1:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3554 (*br*), 2960, 1693; δ_H (360 MHz; $CDCl_3$) 0.82 (6H, d, J = 7.2 Hz, 9,10-H), 2.13 (3H, s, 3'-H), 2.14-2.18 (2H, m, 2,4-H), 2.45 (2H, s, 1'-H), 2.83 (1H, s, 11-H), 4.39 (2H, d, J =

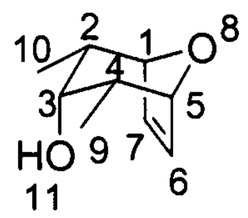
3.7 Hz, 1,5-H), 6.43 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 11.5 (q, 9,10-C), 33.2 (d, 2,4-C), 41.4 (q, 3'-C), 52.0 (t, 1'-C), 75.2 (s, 3-C), 83.1 (d, 1,5-C), 135.4 (d, 6,7-C), 210.3 (s, 2'-C); *m/z* (EI) 210 (M^+; 15%), 148 (36), 43 (100); HRMS calcd for $C_{12}H_{18}O_3Na^+$ 233.1138, found 233.1133.

4-Hydroxy-4-methyl-pent-2-one (248)



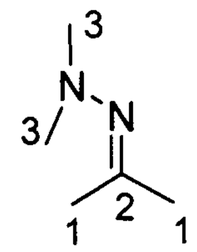
To a solution of dry acetone (5.3 mL, 72.2 mmol) in THF (150 mL) was added dropwise a freshly prepared LDA (THF, 1.9 M, 35.1 mL, 67 mmol) solution at -78 °C. The mixture was stirred for 30 min at -78 °C and then ketone **243** (500 mg, 3.3 mmol) in THF (10 mL) was added. The reaction mixture was stirred for a further 30 min and then allowed to warm to 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography to give the alcohol **248** (350 mg, 93%); R_f 0.23 (4:1 hexane/etnyl acetate); υ_{max} (neat)/cm^{-1} 3432, 2969, 1701; δ_H (360 MHz; $CDCl_3$) 1.26 (3H, s, 1-H), 1.95 (6H, s, 5-H), 2.19 (3H, s, 2-H), 2.64 (2H, s, 3-H), 3.78 (1H, s, 6-H); δ_C (90 MHz, $CDCl_3$) 29.7 (q, 5-C), 32.1 (q, 1-C), 54.2 (t, 3-C), 70.0 (s, 2-C); *m/z* (EI) 116 (M^+; 33%), 99 (80), 59 (100).

2,4-*endo,endo*-Dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-*endo*-3-ol (249)



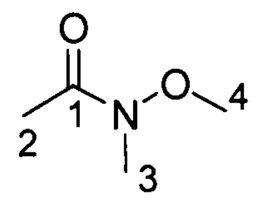
To a solution of ketone **243** (500 mg, 2.29 mmol) in THF (15 mL) was added L-selectride (1.0 M, 6.6 mL, 6.58 mmol) at -78 °C. Stirring was continued at this temperature for 6 h before a solution of sodium hydroxide (3 M, 5 mL) and hydrogen peroxide (27% aq., 7.5 mL) were carefully added. The reaction mixture was allowed to warm to room temperature and the white suspension was partitioned between sodium hydroxide (0.1 M, 45 mL) and dichloromethane (3 x 30 mL). The aqueous phase was extracted with a further two portions of dichloromethane (2 x 20 mL) and the combined organic layers were dried ($MgSO_4$). The organic residue was purified by column chromatography (2:1 60-80 petroleum ether/ethyl acetate) to give the title compound (323 mg, 64%) as a colourless oil. Analytical data for **249** agree with the literature;[154] R_f 0.46 (2:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 3548, 2924, 1625, 1049; δ_H (360 MHz; $CDCl_3$) 0.91 (6H, d, J = 7.4 Hz, 9,10-H), 1.50 (1H, s, 11-H), 2.19-2.24 (2H, m, 2,4-H), 3.66-3.72 (1H, m, 3-H), 4.41 (2H, d, J = 3.2 Hz, 1,5-H), 6.45 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 13.3 (q, 9,10-C), 38.6 (d, 2,4-C), 73.2 (d, 3-C), 82.5 (d, 1,5-C), 136.7 (d, 6,7); *m/z* (EI) 154 (M^+; 10%), 121 (30), 81 (100).

N'-Isopropylidene-*N*,*N*-dimethylhydrazine (250)[128]



A mixture of *N,N*-dimethylhydrazine (30.4 g, 490 mmol) and acetone (31.3 g, 540 mmol) was refluxed for 48 h and then allowed to cool to room temperature. CaH_2 (16.5 g, 392 mmol) followed by NaOH (16.3 g, 408 mmol) were cautiously added. The upper layer was decanted and distilled from CaH_2 under atmospheric pressure, collecting the fraction between 92-95 °C (40 g, 82%); υ_{max} (neat)/cm^{-1} 3510, 2925, 1610; δ_H (360 MHz; $CDCl_3$) 1.90 (3H, s, 1-H), 1.95 (3H, s, 1-H), 2.41 (6H, s, 3-H); δ_C (90 MHz, $CDCl_3$) 18.5 (q), 25.5 (q), 47.4 (q, 3-C), 165.2 (s, 2-C); *m/z* (EI) 100 (M^+; 30%), 86 (60), 58 (100).

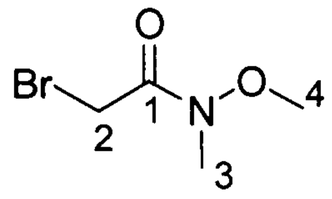
N-Methoxy-*N*-methylacetamide (252)[130]



To a slurry of *N,O*-dimethylhydroxylamine hydrochloride (4.36 g, 44.7 mmol) in DCM (82 mL) was added pyridine (10.1 g, 89.5 mmol) followed by dropwise addition of acetyl bromide (5.01 g, 40.7 mmol) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and then warmed to room temperature. The mixture was stirred at room temperature for 18 h and then quenched with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL), the organic

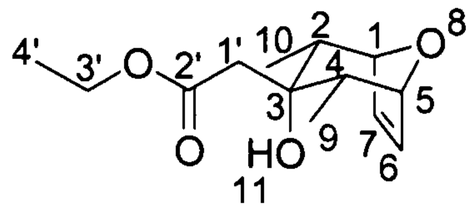
layer dried ($MgSO_4$) and concentrated in vacuo to give amide **252** (1.86 g, 35%) that was used in the next step without further purification; υ_{max} (neat)/cm^{-1} 3000, 2966, 1658, 1471, 1095; δ_H (360 MHz; $CDCl_3$) 2.05 (3H, s, 2-H), 3.11 (3H, s, 3-H), 3.62 (3H, s, 4-H); δ_C (90 MHz, $CDCl_3$) 20.2 (q, 2-C), 32.4 (q, 3-C), 61.5 (q, 4-C), 172.3 (s, 1-C); *m/z* (EI) 103 (M^+; 15%), 61 (99), 43 (100).

2-Bromo-*N*-methoxy-*N*-methylacetamide (253)[130]



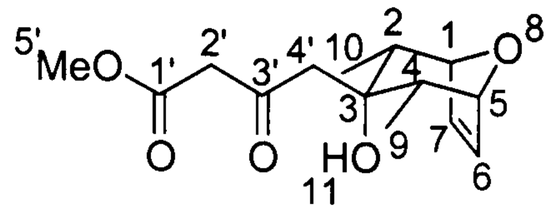
To a slurry of *N,O*-dimethylhydroxylamine hydrochloride (2.66 g, 27.3 mmol) in DCM (50 mL) was added pyridine (6.16 g, 54.5 mmol) followed by dropwise addition of bromoacetyl bromide (5.02 g, 24.8 mmol) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and then warmed to room temperature. The mixture was stirred at room temperature for 18 h and then quenched with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3 x 40 mL), the organic layer dried ($MgSO_4$) and concentrated in vacuo to give amide **253** (643 mg, 15%) that was used in the next step without further purification; υ_{max} (neat)/cm^{-1} 3003, 2975, 1676, 1462, 785; δ_H (360 MHz; $CDCl_3$) 3.24 (3H, s, 3-H), 3.76 (3H, s, 4-H), 4.25 (3H, s, 2-H); δ_C (90 MHz, $CDCl_3$) 33.0 (q, 3-C), 41.2 (t, 2-C), 63.1 (q, 4-C), 175.3 (s, 1-C); *m/z* (EI) 183 (M^+; 37%), 158 (54), 58 (100).

(3-*endo*-Hydroxy-*endo*,*endo*-2,4-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-yl)-acetic acid ethyl ester (255)



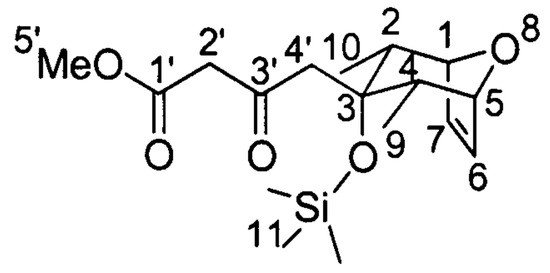
A solution of *n*-BuLi in hexane (2.8 mL, 2.5 M, 6.88 mmol) was added to a solution of diisopropylamine (1.0 mL, 6.88 mmol) in THF (5 mL) at 0 °C. The solution was stirred for 20 min at 0 °C before the temperature was reduced to -78 °C and dry ethyl acetate (670 μL, 6.88 mmol) was added dropwise. The resulting mixture was stirred for 30 min at -78 °C and ketone **243** (530 mg, 3.44 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to -20 °C and then quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL) and the combined ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (5:1 hexane/ethyl acetate), to give compound **255** (354 mg, 43%) as a colourless oil; R_f 0.28 (10% ethyl acetate in 60-80 petroleum ether); υ_{max} (neat)/cm^{-1} 3555, 2962, 1720, 1115, 1644, 1175, 1055; δ_H (360 MHz; $CDCl_3$) 0.92 (6H, d, J = 7.2 Hz, 9,10-H), 1.28 (3H, t, J = 7.1 Hz, 4'-H), 2.22-2.36 (2H, m, 2,4-H), 2.40 (3H, s, 1'-H), 2.67 (1H, s, 11-H), 4.16 (2H, q, J = 14.3 Hz, 3'-H), 4.48 (2H, d, J = 3.7 Hz, 1,5-H), 6.52 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 11.5 (q, 9,10-C), 14.6 (q, 4'-C), 40.8 (d, 2,4-C), 43.8 (t, 3'-C), 61.1 (t, 1'-C), 74.2 (s, 3-C), 83.0 (d, 1,5-C), 135.4 (d, 6,7-C), 172.0 (d, 2'-C); *m/z* (EI) 240 (M^+; 65%), 222 (70), 144 (74), 81 (100); HRMS calcd for $C_{13}H_{20}O_4Na^+$ 263.1254, found 263.1251.

4'-(3-*endo*-Hydroxy-2,4-*endo*,*endo*-dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yl)-3'-oxo-butyric acid methyl ester (256)



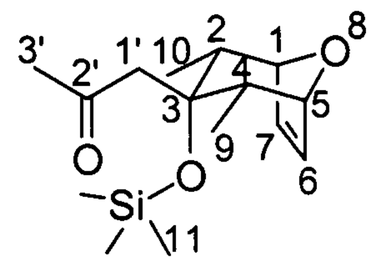
n-BuLi (1.62 mL, 2.5 M, 4.05 mmol) was added to a solution of diisopropylamine (0.6 mL, 3.95 mmol) in THF (20 mL) at 0 °C. The solution was stirred for 20 min before methyl acetoacetate (0.32 mL, 3.95 mmol) was added dropwise. The resulting solution was stirred for 20 min at 0 °C before *n*-BuLi (1.62 mL, 2.5 M, 4.05 mmol) was added. The mixture was stirred at 0 °C for 30 min before ketone **243** (150 mg, 990 μmol) in THF (5 mL) was added at once. The mixture was allowed to warm to room temperature over 2 h and then quenched with 0.1 M HCl solution (5 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil that was purified by column chromatography (3:2 hexane/ethyl acetate) to give the *title compound* (115 mg, 43%) as a colourless oil; R_f 0.24 (3:2 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3564, 2932, 1739, 1710; δ_H (360 MHz; $CDCl_3$) 0.82 (6H, d, J = 7.2 Hz, 9,10-H), 2.16-2.22 (2H, m, 2,4-H), 2.39 (1H, s, 11-H), 2.51 (2H, s, 4'-H), 3.38 (2H, s, 2'-H), 3.60 (3H, s, 5'-H), 4.40 (2H, d, J = 3.7 Hz, 1,5-H), 6.42 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 12.0 (q, 9,10-C), 39.5 (d, 2,4-C), 44.0 (t, 4'-C), 47.5 (t, 2'-C), 52.8 (q, 5'-C), 79.3 (s, 3-C), 83.0 (d, 1,5-C), 133.4 (d, 6,7-C), 174.5 (s, 3'-C), 200.1 (s, 1'C); *m/z* (EI) 268 (M^+; 20%), 153 (40), 85 (100); HRMS calcd for $C_{14}H_{20}O_5Na^+$ 363.1598, found 363.1585.

4'-(2,4-(*endo*,*endo*)-Dimethyl-3-(*endo*)-trimethylsilanyloxy-8-oxa-bicylo[3.2.1]oct-6-en-3-yl)-3'-oxo-butyric acid methyl ester (257)



To a solution of alcohol **256** (121 mg, 450 μmol) and triethylamine (160 μL, 1.13 mmol) in DCM (8 mL) was added trimethylsilyl triflate (130 μL, 680 μmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred until complete disappearance of starting material (by TLC). The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with diethyl ether (3 x 10 mL). The ethereal layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil (125 mg, 82%). The crude product was used in the next step without further purification; R_f 0.52 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2945, 2894, 1746, 1712; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 11-H), 0.82 (6H, d, J = 7.3 Hz, 9,10-H), 2.15-2.20 (2H, m, 2,4-H), 2.56 (2H, s, 4'-H), 3.47 (2H, s, 2'-H), 3.66 (3H, s, 5'-H), 4.41 (2H, d, J = 3.7 Hz, 1,5-H), 6.45 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 3.2 (q, 11-C), 12.1 (q, 9,10-C), 39.4 (d, 2,4-C), 44.1 (t, 4'-C), 47.1 (t, 2'-C), 52.8 (q, 5'-C), 79.2 (s, 3-C), 83.0 (d, 1,5-C), 133.4 (d, 6,7-C), 174.7 (s, 3'-C), 200.2 (s, 1'C); *m/z* (EI) 340 (M^+; 40%), 267 (30), 152 (100); HRMS calcd for $C_{17}H_{28}O_5SiNa^+$ 363.1598, found 363.1585.

1'-(2,4-(*endo*,*endo*)-Dimethyl-3-*endo*-trimethylsilanyloxy-8-oxa-bicylo[3.2.1]oct-6-en-3-yl)-propan-2'-one (258)

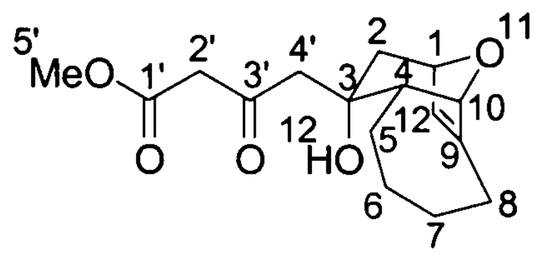


From compound (257). A mixture of ester **257** (235 mg, 690 μmol), DMSO (1.8 mL), NaCl (81.0 mg, 1.38 mmol) and distilled water (50.0 mg, 2.76 mmol) were refluxed for 3 h. After cooling, the reaction mixture was poured into cold water (20 mL), followed by extraction with diethyl ether/hexanes (1:1, 3 x 20 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 hexane/ethyl acetate) to give **258** (71 mg, 40%) as a colorless oil.

From compound (278). To a mixture of alkyne **278** (136 mg, 520 μmol), mercury(II) oxide (112 mg, 520 μmol) and distilled water (30.0 μL, 1.56 mmol) in acetone (5 mL) was added catalytic amount of H_2SO_4 (20 μL, 1 M, 0.04 eq) at room temperature. The resulting mixture was stirred and monitored (by TLC) over 24 h at room temperature and then quenched with water. The aqueous layer was extracted with diethyl ether (3 x 20 mL), and the organic layer washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography (4:1 hexane/ethyl acetate) to give compound **258** (90 mg, 61%) as an oil; R_f 0.35 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2953, 1705, 1105; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 11-H), 0.76 (6H, d, J = 7.2 Hz, 9,10-H), 2.08 (3H, s, 3'-H), 2.16-2.21 (2H, m, 2,4-H), 2.53 (2H, s, 1'-H), 4.30 (2H, d, J = 3.5 Hz, 1,5-H), 6.10 (2H, s, 6,7-H); δ_C (90

MHz, $CDCl_3$) 3.2 (q, 11-C), 12.1 (q, 9,10-C), 33.3 (d, 2,4-C), 39.6 (q, 3'-C), 50.9 (t, 1'-C), 79.2 (s, 3-C), 83.0 (d, 1,5-C), 133.5 (d, 6,7-C), 206.6 (s, 2'-C); *m/z* (EI) 282 (M^+; 20%), 130 (100), 73 (70); HRMS calcd for $C_{15}H_{26}O_3SiNa^+$ 305.1547, found 315.1543.

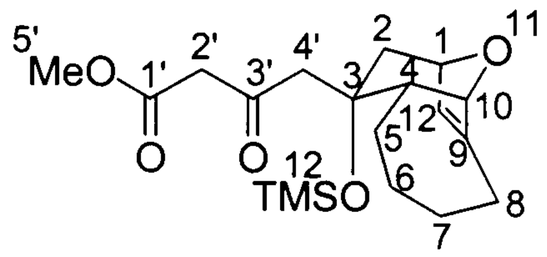
(±)-4'-(3-*endo*-Hydroxy-11-oxa-tricyclo[7.2.1.0^{4,10}]dodec-9(12)-en-3-yl)-3'-oxo-butyric acid methyl ester (259)



To a solution of diisopropylamine (400 μL, 2.81 mmol) in THF (14 mL) was added *n*-BuLi (1.10 mL, 2.5 M, 2.81 mmol) at 0 °C. The solution was stirred for 20 min before methyl acetoacetate (230 μL, 2.81 mmol) was added drop-wise. The resulting solution was stirred for 20 min at 0 °C before *n*-BuLi (1.10 mL, 2.5 M, 2.81 mmol) was added. The mixture was stirred at 0 °C for 30 min before a solution of ketone **195** (100 mg, 560 μmol) in THF (3 mL) was added. The mixture was allowed to warm to room temperature over 2 h and then quenched with 0.1 M HCl (5 mL) solution. The aqueous layer was extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduce pressure to give a residue that was purified by column chromatography (2:1 hexane/ethyl acetate) to give compound **259** (80 mg, 49%) as a colourless oil; R_f 0.55 (2:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3558 (*br*), 2928, 1742, 1710, 1066; δ_H (360 MHz; $CDCl_3$) 1.52-1.60 (4H, m, 5,7-H), 1.62-1.77 (2H, m, 6-H), 1.81 (1H, dd, J = 14.4 and 1.3 Hz, 2-H), 1.96-2.01 (1H, m, 4-H), 2.22-2.25 (1H, m, 2-H), 2.35-2.48 (2H, m, 8-H), 2.75 (1H, d, J = 14.3 Hz, 4'-H), 2.97 (1H, d, J =

14.3 Hz, 4'-H), 3.56 (2H, d, J = 2.2 Hz, 2'-H), 3.74 (3H, s, 5'-H), 4.57 (1H, dd, J = 3.6 and 2.3 Hz, 10-H), 4.70-4.75 (1H, m, 1-H), 5.80-5.85 (1H, m, 12-H); δ_C (90 MHz, $CDCl_3$) 26.6 (t, C), 26.8 (t, C), 27.2 (t, C), 28.3 (t, C), 41.2 (t, C), 45.5 (d, 4-C), 51.7 (t, 4'-C), 52.9 (q, 5'-C), 55.0 (t, 2'-C), 74.5 (s, 3-C), 78.8 (d, 10-C), 82.2 (d, 1-C), 126.0 (d, 12-C), 150.5 (s, 9-C), 168.3 (s, 1'-C), 203.7 (s, 3'-C); *m/z* (EI) 294 (M^+; 100%), 178 (58), 148 (53); HRMS calcd for $C_{16}H_{22}O_5Na^+$ 317.1359, found 317.1356.

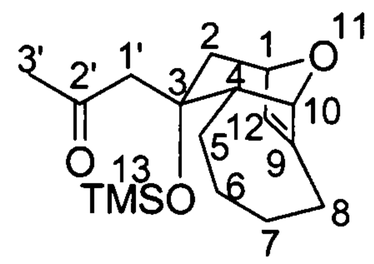
(±)-3'-Oxo-4'-(3-(*endo*)-trimethylsilanyloxy-11-oxa-tricyclo[7.2.1.0^{4,10}]dodec-9(12)-en-3-yl)-butyric acid methyl ester (260)



To a solution of alcohol **259** (121 mg, 410 μmol) and triethylamine (230 μL, 1.65 mmol) in DCM (10 mL) was added trimethylsilyl triflate (200 μL, 1.10 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred until complete disappearance of starting material (by TLC). The reaction was quenched with aqueous $NaHCO_3$ (10 mL), followed by extraction with diethyl ether (3 x 20 mL). The ethereal layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude reaction was purified by column chromatography (2:1 hexane/ethyl acetate) to afford the *title compound* (116.3 mg, 77%); R_f 0.75 (2:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2923, 1745, 1715, 1058; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 12-C), 1.35-1.42 (4H, m, 5,7-H), 1.48-1.63 (2H, m, 6-H), 1.66 (1H, d, J = 14.4, 2-H), 1.68-1.71 (1H, m, 4-H), 1.85 (1H, dd, J = 14.4 and 1.3 Hz, 2-H), 2.13-2.22 (1H, m, 2-H), 2.25-2.33 (2H, m, 8-H), 2.43 (1H, d, J = 14.4 Hz, 4'-H), 2.80 (1H, d, J = 14.4 Hz, 4'-H),

3.30 (2H, s, 2'-H), 3.60 (3H, s, 5'-H), 4.40 (1H, dd, J = 3.6 and 2.4 Hz, 10-H), 4.53-4.83 (1H, m, 1-H), 5.44-5.48 (1H, m, 12-H), δ_C (90 MHz, $CDCl_3$) 3.3 (9H, s, 12-C), 26.5 (t, C), 26.7 (t, C), 27.3 (t, C), 28.1 (t, C), 41.1 (t, C), 45.7 (d, 4-C), 50.0 (t, 4'-C), 51.5 (q, 5'-C), 54.6 (t, 2'-C), 78.0 (s, 3-C), 78.6 (d, 10-C), 81.8 (d, 1-C), 125.5 (d, 12-C), 147.0 (s, 9-C), 167.7 (s, 1'-C), 200.6 (s, 3'-C); *m/z* (EI) 366 (M^+; 49%), 251 (100), 173 (67); HRMS calcd for $C_{19}H_{30}O_5Na^+$ 389.1755, found 389.1752.

(±)-1'-(3-*endo*-Trimethylsilanyloxy-11-oxa-tricyclo[7.2.1.0^{4,10}]dodec-9(12)-en-3-yl)-propan-2-one (261)



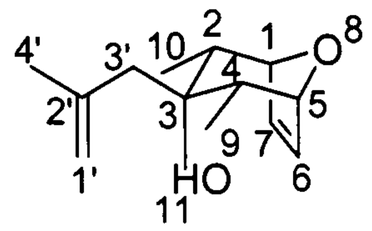
From ester (260). A mixture of ester **260** (190 mg, 520 μmol), DMSO (2.0 mL), NaCl (76.0 mg, 1.30 mmol) and distilled water (38.0 mg, 2.10 mmol) was refluxed for 3 h. After cooling, the reaction mixture was poured onto cold water (10 mL), and then extracted with diethyl ether/hexanes (1:1, 20 mL). The organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 hexane/ethyl acetate) to give compound **261** (67 mg, 50%) as a colourless oil.

From compound (282). To a stirred solution of alkyne **282** (200 mg, 0.69 mmol), mercury(II) oxide (149.3 mg, 0.69 mmol) and distilled water (37 μL, 2.07 mmol) in acetone (3 mL) was added H_2SO_4 (28 μL, 1 M, 0.04 eq) at room temperature. The resulting mixture was stirred and monitored (by TLC) for 4 d at room temperature before water (2 mL) was added. The reaction was extracted with diethyl ether (3 x 5

mL) and the combined ethereal layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a residue that was purified by column chromatography (3:1 hexane/ethyl acetate) to give the *title compound* (32 mg, 15%).

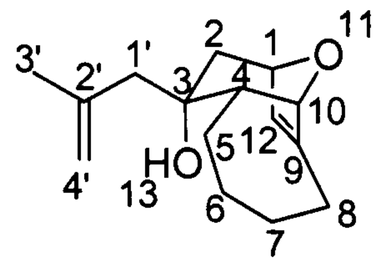
From compound (284). A chilled (0 °C) suspension of **284** (35.0 mg, 92.0 μmol) in dry diethyl ether (1 mL) was treated with methyllithium (115 μL, 1.6 M solution if diethyl ether, 184 μmol). The resulting mixture was allowed to warm to room temperature over 2 h and then water (3 mL) was added. The layers were separated and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 hexane/ethyl acetate) to give **261** (15.6 mg, 55%); R_f 0.47 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2958, 1710, 1622, 1051; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 13-H), 1.36-1.44 (4H, m, 5,7-H), 1.50-1.56 (1H, m, 2-H), 1.56-1.62 (2H, m, 6-H), 2.03 (3H, s, 3'-H), 2.12-2.15 (1H, m, 4-H), 2.20-2.30 (3-H, m, 2,8-H), 2.35 (1H, d, J = 14.1 Hz, 1'-H), 2.69 (1H, d, J = 14.1 Hz, 1'-H), 4.40 (1H, dd, J = 4.0 and 2.5 Hz, 10-H), 4.54 (1H, m, 1-H), 5.48 (1H, m, 12-H), δ_C (90 MHz, $CDCl_3$) 3.3 (q, 13-C), 26.5 (t, C), 26.7 (t, C), 26.9 (t, C), 27.9 (t, C), 33.2 (d, C), 39.5 (t, 2-C), 43.2 (d, 4-C), 55.6 (t, 1'-C), 77.1 (s, 3-C), 77.7 (d, 10-C), 81.9 (d, 1-C), 125.5 (d, 12-C), 146.9 (s, 9-C), 206.9 (s, 2'-C); *m/z* (EI) 308 (M^+; 67%), 221 (100), 107 (96); HRMS calcd for $C_{17}H_{29}O_3SiNa^+$ 331.1718, found 331.1714.

3-(*exo*-2'-Methyl-allyl)-2,4-(*endo*,*endo*)-dimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol) (266)



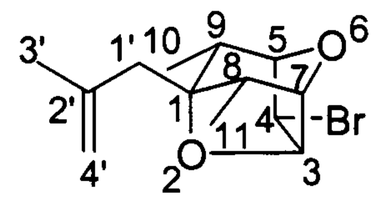
A solution of ketone **243** (426 mg, 2.77 mmol) in anhydrous diethyl ether (2.40 mL) was treated with 2-methylallylmagnesium chloride (THF, 0.5 M, 5.54 mL, 2.77 mmol) at -78 °C. The resulting mixture was allowed to warm to room temperature over 4 h and then quenched with aqueous NH_4Cl (3 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the organic layer washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography (4:1 hexane/ethyl acetate) to afford compound **266** (345 mg, 65%) as a colourless oil; R_f 0.40 (2:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3520, 2929, 1033; δ_H (360 MHz; $CDCl_3$) 0.85 (6H, d, J = 7.3 Hz, 9,10-H), 1.75 (3H, d, J = 2.7 Hz, 4'-H), 2.08 (2H, s, 3'-H), 2.13-2.18 (2H, m, 2,4-H), 4.41 (2H, d, J = 3.7 Hz, 1,5-H), 4.67 (1H, s, 4'-H), 4.82 (1H, d, J = 1.5 Hz, 1'-H), 6.48 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 11.3 (q, 9,10-C), 25.2 (q, 4'-C), 39.9 (d 2,4-C), 47.0 (t, 3'-C), 75.9 (s, 3-C), 83.2 (d, 1,5-C), 116.0 (d, 1'-C), 136.0 (d, 6,7-C), 142.6 (s, 2'-C); *m/z* (EI) 208 (M^+; 3%), 97 (46), 85 (100); HRMS calcd for $C_{13}H_{20}O_2Na^+$ 231.1356, found 231.1350.

(±)-3-(*exo*-2'-Methyl-allyl)-11-oxa-tricyclo[7.2.1.$0^{4,10}$]dodec-9(12)-en-3-ol (267)



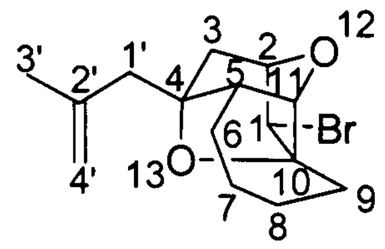
A solution of ketone **195** (210 mg, 1.18 mmol) in THF (4.0 mL) was treated with 2-methylallylmagnesium chloride (THF, 0.5 M, 2.8 mL, 1.42 mmol) at -78 °C. The resulting mixture was allowed to warm to room temperature over 4 h and then quenched with aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude reaction was purified by column chromatography (3:1 hexane/ethyl acetate) to give alcohol **267** (238 mg, 87%) as a pale yellow oil; R_f 0.50 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2932, 1046, 850; δ_H (360 MHz; $CDCl_3$) 1.49-1.67 (5H, m, 5,6,7-H), 1.72-1.80 (4H, m, 3',5-H), 1.90 (1H, d, J = 13.3 Hz, 1'-H), 1.92-1.98 (1H, m, 2-H), 2.10-2.15 (3H, m, 8,13-H), 2.28 (1H, d, J = 13.3 Hz, 1'-H), 2.31-2.35 (1H, m, 2-H), 2.42-2.47 (1H, m, 4-H), 4.51 (1H, dd, J = 4.0 and 2.4 Hz, 10-H), 4.64 (1H, s (br), 4'-H), 4.68 (1H, m, 1-H), 4.82 (1H, dt, J = 2.3 and 1.4 Hz, 4'-H), 5.74-5.80 (1H, m, 12-H); δ_C (90 MHz, $CDCl_3$) 25.2 (q, 3'-C), 25.5 (t), 26.2 (t), 27.0 (t), 28.1 (t), 41.0 (t, 2-C), 45.3 (d, 4-C), 50.9 (t, 1'-C), 74.6 (s, 3-C), 78.9 (d, 10-C), 82.3 (d, 1-C), 115.5 (t, 4'-C), 125.9 (d, 12-C), 142.8 (s, 2'-C), 150.8 (s, 12-C); *m/z* (EI) 234 (M^+; 41%), 179 (100), 81 (61); HRMS calcd for $C_{15}H_{15}O_2Na^+$ 257.1512, found 257.1503.

(±)-(4-*exo*-Bromo-8,9-(*endo,endo*)-dimethyl-1-(*exo*-2'-methyl-allyl))-2,6-dioxa-tricyclo[3.3.1.$0^{3,7}$]nonane (269)



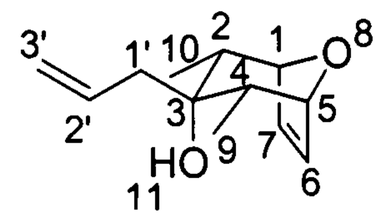
Bromine (24.9 μL, 0.48 mmol) was added to a solution of alcohol **266** (100 mg, 480 µmol) in diethyl ether (3.3 mL) at -78 °C. The mixture was stirred for 4 h while warming to 0 °C. The reaction was quenched with aqueous $NaHCO_3$ (3 mL) and extracted with diethyl ether (3 x 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography (9:1 60-80 petroleum ether/ethyl acetate) to give the *title compound* (124 mg, 89%) as a yellow oil; R_f 0.55 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2931, 1262, 738; δ_H (360 MHz; $CDCl_3$) 0.80 (3H, d, J = 7.1 Hz, 11-H), 0.92 (3H, d, J = 7.1 Hz, 10-H), 1.70 (3H, s, 3'-H), 2.10 (1H, d, J = 15.4 Hz, 1'-H), 2.12-2.16 (1H, m, 9-H), 2.26 (1H, d, J = 15.4 Hz , 1'-H), 2.40 (1H, dt, J = 14.1 and 7.0 Hz, 8-H), 4.11 (1H, dd, J = 4.1 and 1.6 Hz, 4-H), 4.45 (1H, s, 7-H), 4.46 (1H, d, J = 3.7 Hz, 5-H), 4.56 (1H, s, 3-H), 4.72 (1H, s, 4'-H), 4.78 (1H, d, J = 1.4 Hz, 4'-H); δ_C (90 MHz, $CDCl_3$) 11.6 (q), 11.9 (q), 24.3 (q, 3'-C), 37.5 (t, 1'-C), 41.7 (d), 46.7 (d), 52.7 (d, 4-C), 83.5 (d, 7-C), 85.0 (d, 5-C), 85.5 (d, 3-C), 86.4 (s, 1-C), 114.5 (t, 4'-C), 140.5 (s, 2'-C); *m/z* (EI) 286 (M^+; 51%), 178 (100), 149 (33); HRMS calcd for $C_{13}H_{19}O_2{}^{81}BrNa^+$ 311.0440, found 311.0436.

(±)-(1-*exo*-Bromo-4-(*exo*-2'-methylallyl))-12,13-dioxa-tetracyclo[5.3.2.1.0^{10,11}]tridecane (272)



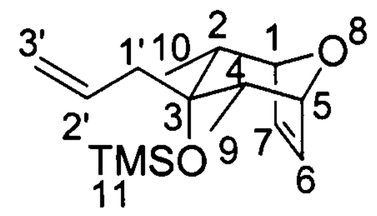
Bromine (13.1 μL, 0.25 mmol) was added to a solution of alcohol **267** (59.0 mg, 250 μmol) in diethyl ether (2.0 mL) at -78 °C. The mixture was stirred for 4 h while warming to 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with diethyl ether (3 x 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography (6:1 60-80 petroleum ether/ethyl acetate) to afford bromoether **272** (59 mg, 75%) as a pale yellow oil; R_f 0.49 (6:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2952, 1030, 780; δ_H (360 MHz; $CDCl_3$) 1.24-1.31 (6H, m, 6,7,8-H), 1.48 (3H, s, 3'-H), 1.60-1.68 (1H, m, 3-H), 1.74-1.86 (3H, m, 3,9-H), 1.98-2.05 (1H, m, 5-H), 2.19 (1H, d, J = 13.7 Hz, 1'-H), 2.28 (1H, d, J = 13.7 Hz, 1'-H), 4.30 (1H, s, 1-H), 4.38 (1H, s, 11-H), 4.35-4.39 (1H, m, 2-H), 4.64 (1H, s, 4'-H), 4.78 (1H, d, J = 1.4 Hz, 4'-H); δ_C (90 MHz, $CDCl_3$) 24.1 (q, 3'-C), 25.3 (t), 24.8 (t), 25.5 (t), 40.8 (t), 41.4 (t, C), 50.5 (d, 5-C), 59.3 (d, 1-C), 83.1 (d, 2-C), 84.4 (d, 11-C), 85.5 (s, 4-C), 93.9 (s, 10-C), 115.1 (t, 4'-C), 141.6 (s, 2'-C); *m/z* (EI) 312 (M^+; 33%), 233 (57), 135 (100); HRMS calcd for $C_{15}H_{21}O_2{}^{79}BrNa^+$ 335.0617, found 335.0613.

(3-*exo*-Allyl-2,4-(*endo*,*endo*)-dimethyl)-8-oxa-bicylo[3.2.1]oct-6-en-3-ol (274)



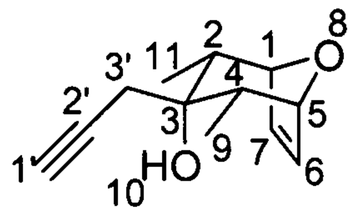
To a solution of ketone **243** (616 mg, 4.01 mmol) in THF (14 mL) was added allylmagnesium chloride (THF, 2.5 M, 3 mL, 7.5 mmol) at -78 °C. The resulting mixture was warmed to 0 °C before aqueous NH_4Cl (3 mL) was added and extracted with diethyl ether (3 x 10 mL). The ethereal layer was dried ($MgSO_4$), and concentrated in vacuo to give a residue that was purified by column chromatography (6:1 hexane/ethyl acetate) to give the *title compound* (526 mg, 68%) as a yellow oil; R_f 0.25 (6:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3543, 3074, 2945, 1050 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.91 (6H, d, J = 7.3 Hz, 9,10-H), 1.86 (1H, s, 11-H), 2.16-2.22 (4H, m, 1',2,4-H), 4.50 (2H, d, J = 3.7 Hz, 1,5-H), 5.02-5.11 (2H, m, 3'-H), 5.72-5.80 (1H, m, 2'-H), 6.58 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 10.8 (q, 9,10-C), 39.3 (d, 2,4-C), 42.7 (t, 1'-C), 75.3 (s, 3-C), 83.2 (d, 1,5-C), 118.6 (t, 3'-C), 134.5 (d, 2'-C), 136.2 (d, 6,7-C); *m/z* (EI) 194 (M^+; 40%), 153 (77), 97 (100); HRMS calcd for $C_{12}H_{18}O_2Na^+$ 217.1191, found 217.1193.

(3-*exo*-Allyl-2,4-(*endo*,*endo*)-dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yloxy)-trimethyl silane (275)



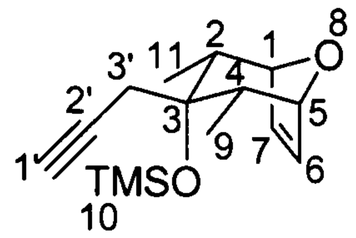
To a solution of alcohol **274** (142 mg, 730 μmol) and triethylamine (260 μL, 1.83 mmol) in DCM (8 mL) was added trimethylsilyl triflate (200 μL, 1.10 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred until complete disappearance of starting material (by TLC). The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to give **275** (125 mg, 82%). The crude product was used without further purification; R_f 0.67 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3075, 2945, 1647, 1644, 1173, 1087; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 11-H), 0.72 (6H, d, J = 7.2 Hz, 9,10-H), 1.98-206 (2H, m, 2,4-H), 2.17 (2H, d, J = 7.4 Hz, 1'-H), 4.30 (2H, d, J = 3.5 Hz, 1,5-H), 4.92-5.01 (2H, m, 3'-H), 5.59-5.68 (1H, m, 2'-H), 6.12 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 3.3 (q, 11-C), 11.8 (q, 9,10-C), 38.7 (d, 2,4-C), 43.1 (t, 1'-C), 79.8 (s, 3-C), 83.2 (d, 1,5-C), 118.5 (t, 3'-C), 133.4 (d, 2'-C), 135.0 (d, 6,7-C); *m/z* (EI) 266 (M^+; 53%), 177 (100), 73 (43); HRMS calcd for $C_{15}H_{26}O_2SiNa^+$ 289.1594, found 289.1585.

3-(*exo*-1'-Propynyl)-2,4-(*endo*,*endo*)-dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-ol (277)



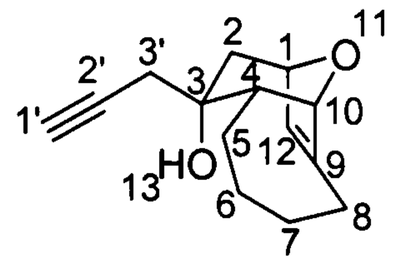
To a suspension of magnesium turnings (151 mg, 6.60 mmol) and mercury(II)chloride (3.05 mg, 0.11 μmol) in dry diethyl ether (5 mL) was added dropwise propargyl bromide (590 μL, 6.60 mmol) at a rate to maintain gentle reflux. To an ice-cold solution of the resulting Grignard reagent was added dropwise a solution of ketone **243** (500 mg, 3.29 mmol) in dry diethyl ether (3 mL) and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (3:1 hexane/ethyl acetate) to give homopropargylic alcohol **277** (332.4 mg, 53%) as a colourless oil; R_f 0.30 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3547, 3246, 2976, 1456; δ_H (360 MHz; $CDCl_3$) 0.92 (6H, d, J = 7.3 Hz, 9,11-H), 1.88 (1H, s, 10-H), 2.07 (1H, t, J = 2.8 Hz, 1'-H), 2.31 (2H, d, J = 2.7 Hz, 3'-H), 2.46-2.54 (2H, m, 2,4-H), 4.54 (2H, d, J = 3.6 Hz, 1,5-H), 6.58 (1H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 10.7 (q, 9,11-C), 28.2 (t, 3'-C), 39.0 (d, 2,4-C), 71.7 (d, 1'-C), 75.3 (s, 2'-C), 81.3 (s, 3-C), 83.01 (d, 1,5-C), 136.1 (d, 6,7-C); *m/z* (EI) 192 (M^+; 15%), 177 (11), 85 (100); HRMS calcd for $C_{12}H_{16}O_2Na^+$ 215.1043, found 215.1055.

(3-(*exo*-1'-Propynyl)-2,4-(*endo*,*endo*)-dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yloxy)-trimethyl silane (278)



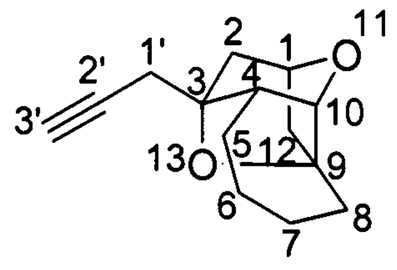
To a solution of alcohol **277** (93.3 mg, 490 μmol) and triethylamine (300 μL, 1.94 mmol) in DCM (5 mL) was added trimethylsilyl triflate (230 μL, 1.26 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred until complete disappearance of starting material (by TLC). The reaction was quenched with aqueous $NaHCO_3$ (5 mL), followed by extraction with diethyl ether (3 x 10 mL). The ethereal layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give the *title compound* (105 mg, 82%), which was used in the next step without further purification; R_f 0.53 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3313, 2926, 1456; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 10-H), 0.74 (6H, d, J = 7.2 Hz, 9,11-H), 1.99 (1H, t, J = 2.7 Hz, 1'-H), 2.30 (2H, d, J = 2.7 Hz, 3'-H), 2.38-42 (2H, m, 2,4H), 4.35 (2H, d, J = 3.5 Hz, 1,5-H), 6.13 (1H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 3.2 (10-C), 12.0 (q, 9,11-C), 29.1 (t, 3'-C), 39.0 (d, 2,4-C), 71.8 (d, 1'-C), 79.4 (s, 2'-C), 81.5 (d, 3-C), 83.0 (d, 1,5-C), 133.3 (d, 6,7-C); *m/z* (EI) 264 (M^+; 4%), 225 (97), 73 (63); HRMS calcd for $C_{15}H_{24}O_2SiNa^+$ 287.1433, found 287.1428.

(±)-3-(*exo*-1'-Propynyl)-11-oxa-tricyclo[7.2.1.$0^{4,10}$]dodec-9(12)-en-3-ol (279)



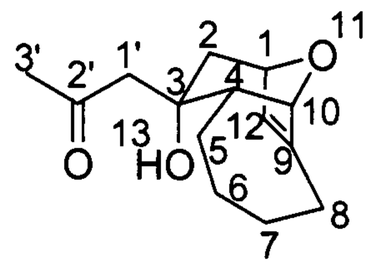
To a suspension of magnesium turnings (99.0 mg, 4.21 mmol) and mercury(II) chloride (1.94 mg, 7.16 μmol) in dry diethyl ether (3 mL) was added dropwise propargyl bromide (330 µL, 4.21 mmol) at a rate to maintain gentle reflux. To an ice-cold solution of the resulting Grignard reagent was added dropwise a solution of ketone **195** (300 mg, 1.69 mmol) in dry diethyl ether (3 mL) and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the resulting mixture extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (3:1 hexane/ethyl acetate) to give homopropargylic alcohol **279** (323 mg, 88%) as a colourless oil; R_f 0.28 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3420 (*br*), 3237, 2926, 1457; δ_H (360 MHz; $CDCl_3$) 1.49-69 (6H, m, 5,6,7-H), 1.85-1.92 (1H, m, 2-H), 2.07 (1H, t, J = 2.7 Hz, 1'-H), 2.19 (1H, *br*, 13-H), 2.23-2.28 (2H, m, 3'-H), 2.31-2.36 (3H, m, 2,8-H), 2.42-2.48 (1H, m, 4-H), 4.54 (1H, d, J = 3.9 Hz, 10-H), 4.69-4.73 (1H, m, 1-H), 5.80 (1H, s (br), 12-H); δ_C (90 MHz, $CDCl_3$) 25.9 (t, 6-C), 26.7 (t, 7-C), 26.9 (t, 5-C), 27.9 (t, 3'-C), 32.6 (t, 2-C), 40.2 (t, 8-C), 43.3 (d, 4-C), 71.5 (d, 1'-C), 74.1 (s, 2'-C), 78.8 (d, 10-C), 81.2 (s, 3-C), 81.9 (d, 1-C), 125.9 (d, 12-C), 151.0 (s, 9-C); *m/z* (EI) 218 (M^+; 100%), 179 (49), 107 (75) ; HRMS calcd for $C_{14}H_{18}O_2Na^+$ 241.1199, found 241.1216.

(±)-3-*exo*-Prop-2'-ynyl-11,13-dioxa-tetracyclo[5.3.2.1.0^{9,10}]tridecane (280)



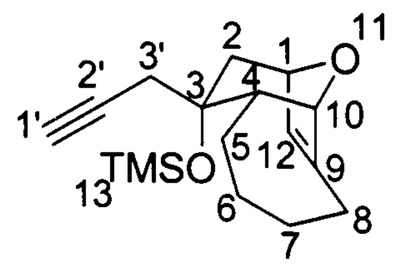
A solution of mercury(II) oxide (1.30 mg, 5.87 μmol, 1 mol%), Tf_2O (1 μL, 5.87 mmol, 1 mol%), TMU (1.40 μL, 11.7 μmol, 2 mol%), distilled water (32.0 mg, 1.77 mmol) and DCM (0.2 mL) in acetonitrile (0.3 mL) was added to alkyne **279** (128 mg, 590 μmol) at room temperature. The resulting mixture was stirred for 24 h at room temperature and aqueous NH_4Cl (2 mL) and $NaHCO_3$ (3 mL) were added. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined ethereal layer was washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduce pressure to give a residue which was purified by column chromatography (3:1 hexane/ethyl acetate) to yield first compound **280** (4 mg, 3%) as colourless oil, followed by alkyne **279** (70 mg, 54%) and finally β-hydroxy ketone **281** (16 mg, 12%). Analytical data for **280**: R_f 0.51 (2:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3237, 2962, 1438, 1118; δ_H (360 MHz; $CDCl_3$) 1.47-1.53 (4H, m, 6,7-H), 1.66-1.73 (4H, m, 5,8-H), 1.90-1.96 (2H, m, 12-H), 2.03 (1H, d, J = 2.8 Hz, 2-H), 2.19 (1H, t, J = 2.5 Hz, 3'-H), 2.20-2.29 (2H, m, 1'-H), 2.31-2.36 (2H, m, 2,4-H), 4.26 (1H, s (br), 10-H), 4.49 (1H, t, J = 4.2, 1-H), δ_C (90 MHz, $CDCl_3$) 24.1 (t, C), 25.4 (t, C), 26.6 (t, C), 30.0 (t, C), 38.4 (t, C), 44.1 (t, C), 50.1 (d, 4-C), 66.3 (t, C), 70.1 (d, 3'-C), 78.5 (s, 2'-C), 80.3 (s, 3-C), 84.5 (d, 1-C), 85.2 (d, 10-C), 92.6 (s, 9-C); *m/z* (EI) 218 (M^+; 53.3%), 177 (36), 136 (100); HRMS calcd for $C_{14}H_{18}O_2Na^+$ 241.1199, found 241.1186.

(±)-1'-(3-(*endo*)-Hydroxy-11-oxa-tricyclo[7.2.1.$0^{4,10}$]dodec-9(12)-en-3-yl)-propan-2'-one (281)



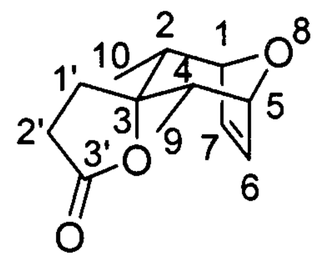
To a stirred solution of alkyne **282** (200 mg, 690 μmol), mercury(II) oxide (149 mg, 690 μmol) and distilled water (37.0 μL, 2.07 mmol) in acetone (3 mL) was added H_2SO_4 (28 μL, 1 M, 0.04 eq) at room temperature. The resulting mixture was stirred for 4 d at room temperature before water (2 mL) was added. The reaction was extracted with diethyl ether (3 x 5 mL) and the combined ethereal layer was washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduce pressure to give a residue which was purified by column chromatography (3:1 hexane/ethyl acetate) to give compound **281** (73 mg, 45% over two steps) as a colourless oil; R_f 0.37 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3473, 2910, 1699; δ_H (360 MHz; $CDCl_3$) 1.32-1.54 (4H, m, 5,7-H), 1.56-1.67 (2H, m, 6-H), 1.76 (1H, d, J = 15.3 Hz, 2-H), 1.88-1.95 (1H, m, 4-H), 2.05 (1H, dd, J = 15.3 and 3.9 Hz, 2-H), 2.11 (3H, s, 3'-H), 2.16 (1H, d, J = 15.4 Hz 1'-H), 2.29-2.37 (2H, m, 8-H), 2.72 (1H, d, J = 15.4 Hz, 1'-H), 2.91 (1H, s, 13-H), 4.35 (1H, d, J = 3.9 Hz, 10-H), 4.49-4.54 (1H, m, 1-H), 5.59 (1H, s (br), 12-H), δ_C (90 MHz, $CDCl_3$) 26.5 (t, C), 27.0 (t, C), 27.9 (t, C), 32.9 (d, 3'-C), 40.9 (t, 2-C), 45.2 (d, 4-C), 55.5 (t, 1'-C), 73.9 (s, 3-C), 78.7 (d, 10-C), 82.1 (d, 1-C), 125.6 (d, 12-C), 149.3 (s, 9-C), 210.4 (s, 2'-C); *m/z* (EI) 236 (M^+; 100%), 178 (80), 148 (87); HRMS calcd for $C_{14}H_{20}O_3Na^+$ 259.1305, found 259.1303.

(±)-(3-(*exo*-1'-Propynyl)-11-oxa-tricyclo[7.2.1.$0^{4,10}$]dodec-9(12)-en-3-yloxy) trimethyl silane (282)



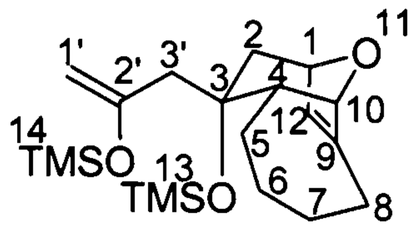
To a solution of alcohol **279** (200 mg, 920 μmol) and triethylamine (510 μL, 3.67 mmol) in DCM (23 mL) was added trimethylsilyl triflate (430 μL, 2.39 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred until complete disappearance of starting material (by TLC). The reaction was quenched with aqueous $NaHCO_3$ (5 mL), and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The ethereal layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil that was purified by column chromatography (5:1 hexane/ethyl acetate) to give the title compound (220.2 mg, 82%) as a colourless oil; R_f 0.63 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3236, 2926, 1456; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 13-H), 1.36-1.44 (4H, m, 6,7-H), 1.47-1.59 (2H, m, 5-H), 1.60-1.76 (2H, m, 8-H), 1.96 (1H, t, J = 2.7 Hz, 1'-H), 2.13-2.41 (4H, m, 3',2,4-H), 4.44 (1H, d, J = 3.9 Hz, 10-H), 4.54-4.59 (1H, m, 1-H), 5.49 (1H, s (br), 12-H), δ_C (90 MHz, $CDCl_3$) 3.2 (q, 13-C), 26.4 (t, C), 26.5 (t, C), 27.0 (t, C), 27.9 (t, C), 33.6 (t, C), 38.9 (t, C), 42.5 (d, 4-C), 66.4 (s, C), 71.9 (d, 1'-C), 78.7 (d, 10-C), 81.8 (d, 1-C), 82.0 (s, 3-C), 125.1 (d, 12-C), 147.0 (s, 9-C); *m/z* (EI) 290 (M^+; 21%), 251 (91), 73 (100); HRMS calcd for $C_{17}H_{26}O_2SiNa^+$ 313.1594, found 313.1593.

(±)-2,4-(*endo,endo*)-Dimethyl-3-dihydro-furan-2'-one-8-oxa-bicyclo[3.2.1]oct-6-ene (283)



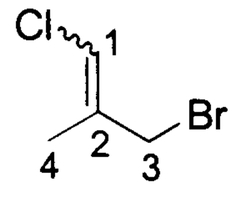
To a stirred solution of alkyne **277** (134 mg, 700 μmol), mercury(II) oxide (151 mg, 700 μmol) and distilled water (37 μL, 2.1 mmol) in acetone (1.5 mL) was added H_2SO_4 (28 μL, 1 M, 0.04 eq) at room temperature. The resulting mixture was stirred for 1 h at room temperature before water (2 mL) was added. The reaction was extracted with diethyl ether (3 x 5 mL) and the combined ethereal layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduce pressure to give a residue that was purified by column chromatography (1:1 hexane/ethyl acetate) to yield the title compound (110 mg, 76%); R_f 0.4 (1:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2957, 1754, 1110; δ_H (360 MHz; $CDCl_3$) 0.79 (6H, d, J = 7.2 Hz, 9,10-H), 1.98-2.04 (4H, m, 2,4,1'-H), 2.38 (2H, t, J = 9.1 Hz, 2'-H), 4.41 (2H, d, J = 3.3 Hz, 1,5H), 6.26 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 10.4 (q, 9,10-C), 28.45 (t, 1'-C), 33.7 (t, 2'-C), 44.6 (d, 2,4-C), 82.6 (d, 1,5-C), 87.9 (s, 3-C), 133.4 (d, 6,7-C), 178.2 (s, 3'-C); *m/z* (EI) 208 (M^+; 61.3%), 179 (20.5), 113 (100); HRMS calcd for $C_{12}H_{16}O_3$ 208.1083, found 208.1094.

(±)-3-(*endo*)-Trimethylsilanyloxy-3'-(2'-trimethylsilanyloxy-ally)-11-oxatricyclo [7.2.1.0^{4,10}]dodec-9(12)-ene (284)



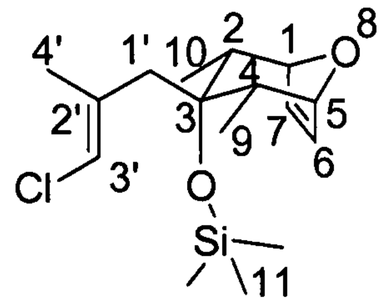
To a solution of hydroxyketone **281** (50.0 mg, 210 μmol) and triethylamine (120 μL, 850 μmol) in DCM (2 mL) was added trimethylsilyl triflate (100 μL, 550 μmol) at 0 °C. The resulting mixture was stirred for 2 h while warming to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the aqueous layer extracted with diethyl ether (3 x 10 mL). The ethereal layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a residue that was purified by column chromatography (10:1 hexane/ethyl acetate) to give the title compound (55.9 mg, 70%) as a pale yellow oil; R_f 0.75 (5:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2966, 1643, 1250; δ_H (360 MHz; $CDCl_3$) -0.12 (9H, s, 13-H), 0.00 (9H, s, 14-H), 1.17-1.34 (4H, m, 5,7-H), 1.45-1.51 (2H, m, 6- H), 1.52-1.66 (1H, m, 2-H), 1.84 (1H, d, J = 13.1 Hz, 3'-H), 2.14 (1H, d, J = 13.1 Hz, 3'-H), 2.16-2.28 (4H, m, 2,4,8-H), 3.81 (1H, s, 1'-H), 3.91 (1H, s, 1'-H), 4.28 (1H, d, J = 3.9 Hz, 10-H), 4.38-4.44 (1H, m, 1-H), 5.35 (1H, s (br), 12-H), δ_C (90 MHz, $CDCl_3$) 0.3 (q, 13-C), 2.9 (q, 14-C), 26.1 (t, C), 26.2 (t, C), 27.6 (t, C), 38.7 (t, C), 41.0 (d, 4-C), 49.7 (t, 3'-C), 77.7 (s, 3-C), 78.5 (d, 10-C), 81.6 (d, 1-C), 93.9 (t, 1'-C), 124.8 (d, 12-C), 146.3 (s, 9-C), 156.2 (s, 2'-C); *m/z* (EI) 380 (M^+; 2%), 251(100), 73 (68); HRMS calcd for $C_{20}H_{36}O_3Si_2Na^+$ 403.2095, found 403.2099.

3-Bromo-1-chloro-2-methylpropene (289) [144b]

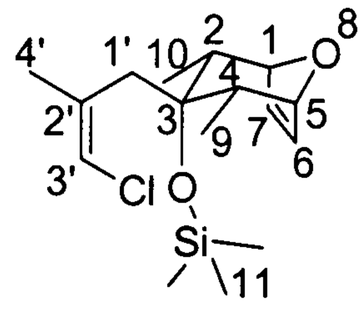


To a stirred solution of 1-chloro-2-methylpropene (2.50 g, 27.6 mmol) in dry carbon tetrachloride (17 mL) were added *N*-bromosuccinimide (3.24 g, 18.1 mmol) and benzoyl peroxide (13.4 mg, 0.55 μmol). The mixture was heated under reflux for 2 h and the succinimide removed by suction filtration and washed with carbon tetrachloride (2 x 4 mL). The combined organic filtrates were concentrated in vacuo to give a yellow oil that was purified by distillation under reduce pressure (0.5 mm/Hg, 25-28 °C) to give compound **289** (2.1 g, 67%) as a colourless oil; (υ_{max} (neat)/cm^{-1} 3053, 2986, 1642, 1259, 930, 739; δ_H (360 MHz; $CDCl_3$) 1.85 (3H, s, 4-H), 3.91 (2H, s, 3-H), 6.20 (1H, d, J = 1.1 Hz, 1-H); δ_C (90 MHz, $CDCl_3$) 15.9 (q, 4-C), 36.5 (t, 3-C), 118.7 (d, 1-C), 135.7 (s, 2-C); *m/z* (EI) 355 ($[M_2+NH_4]^+$; 100%), 338 (35).

(*E*)-3'-(2,4-(*endo*,*endo*)-Dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yloxy-1'-(3'-chloro-2'-methyl-allyl)) trimethyl silane (290a) and (*Z*)-3'-(2,4-(*endo*,*endo*)-Dimethyl-8-oxa-bicylo[3.2.1]oct-6-en-3-yloxy)-1'-(3'-chloro-2'-methyl-allyl)) trimethyl silane (290b)



290a



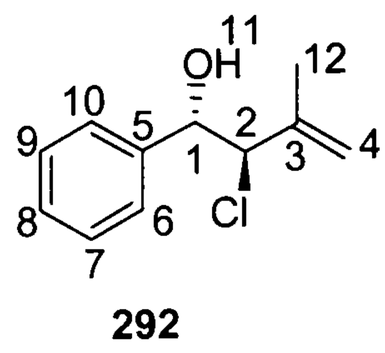
290b

n-BuLi (800 μL, 2.3 M in hexane, 1.84 mmol) was added dropwise at 0 °C to diisopropylamine (0.26 mL, 1.84 mmol) in THF (5.3 mL). After stirring for an additional 45 min, the mixture was cooled to -78 °C, and then (chloromethyl)triphenylphosphonium chloride (640 mg, 1.84 mmol) was added portionwise. After stirring for 10 min at -78 °C, the mixture was warmed to room temperature for 10 min and then cooled to -78 °C before a solution of ketone **258** (236.4 mg, 0.84 mmol) in THF (5.3 mL) was added over 5 min. The mixture was stirred and allowed to warm to room temperature over 18 h, and then saturated aqueous NH_4Cl (3 mL) was added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (9:1 hexane/ethyl acetate) to give the E-isomer **290a** (77 mg, 30%) followed by the Z-isomer **290b** (70 mg, 27%) in 56% overall yield. Analytical data for **290a**: R_f 0.32 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm $^{-1}$ 2954, 1249, 832 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 11-H), 0.75 (6H, d, ^3J 7.16 Hz, 9,10-H), 1.75 (3H, d, ^3J 1.25 Hz, 4'-H), 1.97-2.02 (2H, m, 2,4-H), 2.20 (2H, s, 1'-H), 4.31 (2H, d, ^3J

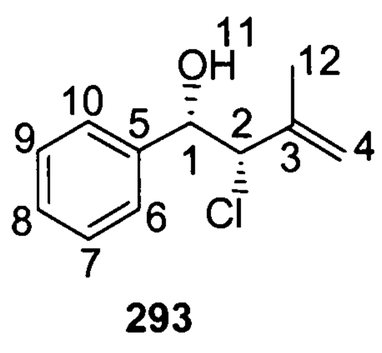
3.52 Hz, 1,5-H), 5.72 (1H, d, ^2J 0.81 Hz, 3'-H), 6.11 (2H, s, 6,7-H); δ_C (90 MHz, $CDC1_3$) 3.3 (q, 11-C), 12.0 (q, 9,10-C), 19.5 (q, 4'-C), 38.7 (d, 2,4-C), 45.2 (t, 1'-C), 80.3 (s, 3-C), 83.1 (d, 1,5-C), 117.5 (d, 6,7-C), 133.5 (d, 3'-C), 135.1 (s, 2'-C); *m/z* (EI) 314 (M^+; 100%), 241 (48), 206 (41); HRMS calcd for $C_{16}H_{27}O_2{}^{35}ClSiNa^+$ 337.1330, found 337.1339.

Analytical data for **290b**: R_f 0.32 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm $^{-1}$ 2958, 1252, 835 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 11-H), 0.77 (6H, d, ^3J 7.12 Hz, 9,10-H), 1.72 (3H, d, ^3J 1.43 Hz, 4'-H), 1.91-2.16 (2H, m, 2,4-H), 2.34 (2H, s, 1'-H), 4.27 (2H, d, ^3J 3.62 Hz, 1,5-H), 5.82 (1H, d, ^2J 1.18 Hz, 3'-H), 6.09 (2H, s, 6,7-H); δ_C (90 MHz, $CDC1_3$) 3.3 (q, 11-C), 12.7 (q, 9,10-C), 23.9 (q, 4'-C), 39.7 (d, 2,4-C), 41.1 (t, 1'-C), 81.0 (s, 3-C), 83.1 (d, 1,5-C), 116.5 (d, 6,7-C), 133.4 (d, 3'-C), 135.0 (s, 2'-C); *m/z* (EI) 314 (M^+; 100%), 241 (50), 206 (40); HRMS calcd for $C_{16}H_{27}O_2{}^{35}ClSiNa^+$ 337.1361, found 337.1355.

(±)-(*anti*-2-Chloro-3-methyl-1-phenyl)-but-3-en-1-ol (292) and (±)-(*syn*-2-Chloro-3-methyl-1-phenyl)-but-3-en-1-ol (293)



292



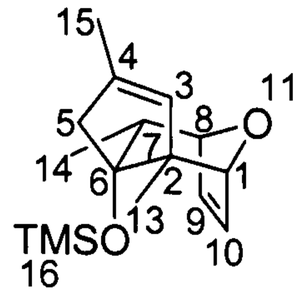
293

A solution of indium (358 mg, 3.12 mmol) in DMF (2 mL) was treated with vinyl chloride **289** (527 mg, 3.12 mmol) in DMF (1.5 mL) at room temperature. The resulting mixture was stirred for 1 h, before a solution of benzaldehyde (221 mg, 2.08

mmol) in DMF was added at room temperature. The combined mixture was stirred for 24 h and then quenched with hydrochloric acid (0.1 M). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the organic layer washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude reaction was purified by column chromatography (20:1 hexane/ethyl acetate) to afford first compound **292** (100 mg, 25%) as an oil, followed by compound **293** (60 mg, 15%). Analytical data for compound **292**: R_f 0.48 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3548 (*br*), 2914, 2847, 1431, 1060; δ_H (360 MHz; $CDCl_3$) 1.80 (3H, s, 12-H), 2.87 (1H, d, J= 2.9 Hz, 11-H), 4.63 (1H, d, J = 8.4 Hz, 2-H), 4.81-4.84 (2H, m, 4-H), 4.87 (1H, s, 1-H), 7.32-7.36 (5H, m, 6,7,8,9,10-H); δ_C (90 MHz, $CDCl_3$) 18.7 (q, 12-C), 74.0 (d, 2-C), 76.6 (d, 1-C), 117.7 (t, 4-C), 127.3 (d), 128.8 (d), 128.9 (d), 139.6 (s), 141.4 (s); *m/z* (EI) 179 ($M-H_2O^+$; 40%), 107 (85), 79 (100), 77 (52); HRMS calcd for $C_{11}H_{13}O^{35}ClNa^+$ 219.0554, found 219.0552.

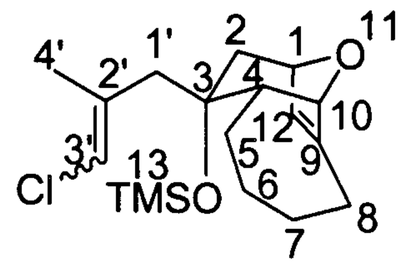
Analytical data for **293**: R_f 0.40 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3540 (*br*), 2916, 1451, 1020; δ_H (360 MHz; $CDCl_3$) 1.94 (3H, s, 12-H), 2.32 (1H, d, J= 2.7 Hz, 11-H), 4.51 (1H, d, J = 8.1 Hz, 2-H), 4.83 (1H, dd, J = 8.1 and 2.7 Hz, 1-H), 5.10-5.14 (2H, m, 4-H), 7.35-7.46 (5H, m, 6,7,8,9,10-H); δ_C (90 MHz, $CDCl_3$) 18.0 (q, 12-C), 70.0 (d, 2-C), 76.1 (d, 1-C), 118.1 (t, 4-C), 127.5 (d), 128.8 (d), 129.4 (d), 140.4 (s), 142.1 (s); *m/z* (EI) 179 ($M-H_2O^+$; 52%), 107 (83), 79 (100), 77 (45) ; HRMS calcd for $C_{11}H_{13}O^{35}ClNa^+$ 219.0547, found 219.0542.

(±)-(2-(*endo*),4,7-(*endo*)-trimethyl-11-oxa-tricyclo[6.2.1.$0^{2,6}$]undeca-3,9-dien-(*endo*)-6-yloxy) trimethyl silane (294)



Sodium bis(trimethylsilyl)amide (3.1 mL, 1.0 M in toluene, 3.07 mmol) was added dropwise to a mixture of vinyl chlorides **290a** and **290b** (275 mg, 880 μmol) in dry diethyl ether (7 mL) at rt. The mixture was stirred for 18 h at rt before saturated aqueous NH_4Cl (3 mL) was added, followed by water (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (3:1 hexane/ethyl acetate) to give cyclopentene **294** (171 mg, 70%) as a colourless oil; R_f 0.20 (3:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2916, 1247, 1041; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 16-H), 0.70 (3H, s, 13-H), 0.73 (3H, d, J = 7.3 Hz, 14-H), 1.58 (3H, s, 15-H), 1.78-1.85 (1H, m, 7-H), 1.89 (1H, d, J = 14.8 Hz, 5-H), 2.32 (1H, d, J = 14.8 Hz, 5-H), 4.25 (2H, dd, J = 1.6 and 1.0 Hz, 8-H), 4.27 (1H, d, J = 1.0 Hz, 1-H), 5.29 (1H, s, 3-H), 6.06-6.12 (2H, m, 9,10-H); δ_C (90 MHz, $CDCl_3$) 2.7 (q, 16-C), 12.5 (q, 14-C), 17.9 (q, 13-C), 20.4 (q, 15-C), 40.2 (d, 7-C), 49.3 (t, 5-C), 52.2 (s, 2-C), 82.0 (d, 6-C), 83.9 (d, 1-C), 84.7 (s, 8-C), 132.3 (d, 3-C), 132.9 (d, 9-C), 133.7 (d, 10-C), 136.2 (s, 4-C); *m/z* (EI) 278 (M^+; 14%), 183 (100), 73 (98); HRMS calcd for $C_{16}H_{26}O_2SiNa^+$ 301.1594, found 301.1587.

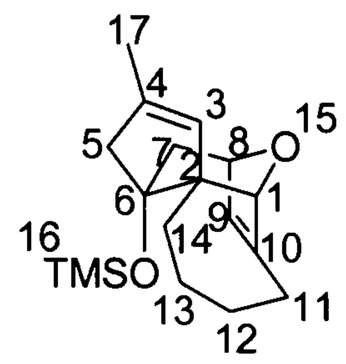
(±)-(3-(*exo*)- 1'-(3'-chloro-2'-methyl-allyl)-11-oxa-tricyclo[7.2.1.0^{4,10}]dodec-9-en-3-yloxy) trimethyl silane (295)



n-BuLi (170 μL, 2.4 M in hexane, 410 μmol) was added dropwise at 0 °C to diisopropylamine (57.1 μL, 410 μmol) in THF (3 mL). After stirring for an additional 45 min, the mixture was cooled to -78 °C, and then (chloromethyl)triphenylphosphonium chloride (141 mg, 410 μmol) was added portionwise. After stirring for 10 min at -78 °C, the mixture was warmed to room temperature for 10 min and then cooled to -78 °C before a solution of ketone **261** (57.0 mg, 190 μmol) in THF (3 mL) was added over 5 min. The mixture was stirred and allowed to warm to room temperature over 18 h, and then saturated aqueous NH_4Cl (2 mL) was added. The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (6:1 hexane/ethyl acetate) to give a mixture of isomers of the title compound (39 mg, 60%) R_f 0.65 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 2953, 1175, 830; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 13-H), 1.34-48 (4H, m, 5,7-H), 1.57-67 (3H, m, 2,6-H), 1.72 (3H, s, 4'-H), 1.75-1.81 (1H, m, 4-H), 1.99-2.08 (2-H, m, 1',2-H), 2.11-2.20 (2H, m, 8-H), 2.34 (1H, d, J = 13.8 Hz, 1'-H), 4.39 (1H, d, J = 4.0 Hz, 10-H), 4.50.4.55 (1H, m, 1-H), 5.48 (1H, s (br), 12-H), 5.71 (1H, s, 3'-H), δ_C (90 MHz, $CDCl_3$) 3.3 (q, 13-C), 23.9 (q, 4'-C), 26.6 (t, C), 26.8 (t, C), 26.9 (t, C), 28.0 (t, C), 40.0 (t, C), 42.9 (d, 4-C), 45.3 (t, C), 78.8 (d, 10-C), 79.4 (s, 3-C), 82.1 (d, 1-C), 116.3 (d, 3'-C), 125.3

(d, 12-C), 135.6 (s, 2'-C), 146.8 (s, 9-C); *m/z* (EI) 363 ([M+Na] $^{+}$; 100%), 340 (20), 290 (40); HRMS calcd for $C_{18}H_{29}O_2SiClNa^{+}$ 363.1341, found 363.1351.

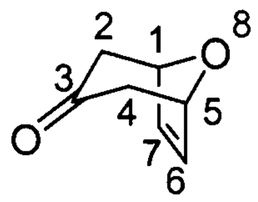
(±)-6-*endo*-Trimethylsilanyloxy-4-methyl-15-oxa-tetracyclo[10.2.1.0^{2,6}]pentadeca-3,9-diene (296)



A solution of vinyl chloride **295** (39.0 mg, 110 μmol) in dry diethyl ether (2 mL) was treated with sodium bis(trimethylsilyl)amide (460 μL, 1.0 M in toluene, 460 μmol) at room temperature. The mixture was stirred for 18 h at room temperature and then saturated aqueous NH_4Cl (1.5 mL) was added, followed by water (2 mL) and ethyl acetate (3 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a residue that was purified by column chromatography (5:95 ethyl acetate/hexane) to give cyclopentene **296** (22 mg, 63%) as a colorless oil; R_f 0.20 (5% ethyl acetate in hexane); υ_{max} (neat)/cm^{-1} 3055, 2952, 1649, 1446, 1052, 920; δ_H (360 MHz; $CDCl_3$) 0.00 (9H, s, 16-H), 0.91-1.00 (1H, m, 14-H), 1.29-1.38 (1H, m, 14-H), 1.40-1.58 (2H, m, 13- H), 1.65 (3H, s, 17-H), 1.72-1.74 (2H, m, 12-H), 1.75-1.83 (2H, m, 7-H), 1.94 (1H, d, J = 14.4 and 1.7 Hz, 5-H), 2.32-2.43 (2H, m, 11-H), 2.63 (1H, d, J = 14.4 Hz, 5-H), 4.41 (1H, s, 1-H), 4.51-4.56 (1H, m, 8-H), 5.22 (1H, q, J = 1.8 Hz, 9-H), 5.55 (1H, d, J = 1.7 Hz, 3-H), δ_C (90 MHz, $CDCl_3$) 2.6 (q, 16-C), 17.8 (q, 17-C), 25.9 (t, 14-C), 27.3 (t, 13-C), 28.1 (t, 11-C), 35.3 (t, 12-C), 40.9

(t, 7-C), 52.5 (t, 5-C), 55.2 (s, 2-C), 78.3 (d, 8-C), 83.0 (s, 6-C), 83.2 (d, 1-C), 125.7 (d, 9-C), 134.2 (d, 3-C), 135.3 (s, 4-C), 146.4 (s, 10-C); *m/z* (EI) 304 (M^+; 100%), 181(36), 73 (62); HRMS calcd for $C_{15}H_{20}O_2$ 304.1867, found 304.1869.

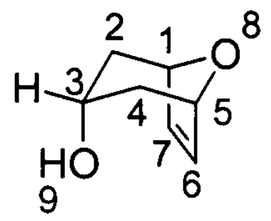
8-Oxa-bicyclo[3.2.1]oct-6-en-3-one (319)



A solution of $NaOCH_2CF_3$ (50.0 mL, 100 mmol) in CF_3CH_2OH (50 mL) and 1,3,3-trichloroacetone (5.2 mL, 50 mmol) were added separately via syringe to furan (7.01 g, 2.06 mmol) in CF_3CH_2OH (20 mL) over 15 min at 0 °C. The reaction was stirred overnight at room temperature and then quenched with water (5 mL). The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a residue that was dissolved in methanol (200 mL) and added to a solution of Zn (32.7 g, 500 mmol) and CuI (17.0 g, 150 mmol) in methanol (50 mL). The mixture was stirred at room temperature for 24 h and then filtered through Celite (20 g). The filtrate was concentrated to give a residue that was dissolved in 5% HCl solution. The aqueous layer was extracted with diethyl ether (3 x 35 mL) and once with ethyl acetate (30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a residue that was purified by column chromatography (4:1 60-80 petroleum ether/ethyl acetate) to give ketone **319** (3.3 g, 53% over two steps). Analytical data of **319** agree with literature;[154] R_f 0.57 (4:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 2937, 1724, 1641, 1115; δ_H (360 MHz; $CDCl_3$) 2.35 (2H, d, J = 16.5 Hz, 2,4-H), 2.78 (2H, dd, J = 16.9 and 5.1 Hz, 2,4-H),

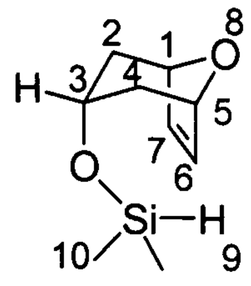
5.05 (2H, d, J = 5.1 Hz, 1,5-H), 6.28 (1H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 38.5 (t, 2,4-C), 78.1 (d, 1,5-C), 136.2 (d, 6,7-C), 207.3 (s, 3-C); *m/z* (EI) 124 (M^+; 58%), 106 (30), 68 (100).

8-Oxa-bicyclo[3.2.1]oct-6-en-(*endo*)-3-ol (321)



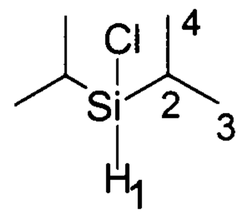
To a solution of ketone **319** (300 mg, 2.40 mmol) in THF (15 mL) was added L-selectride (1.0 M, 4.8 mL) at -78 °C. Stirring was continued at this temperature for 6 h before a solution of sodium hydroxide (3 M, 3 mL) and hydrogen peroxide (27% aq., 2 mL) were carefully added. The reaction mixture was allowed to warm to room temperature and the white suspension was partitioned between sodium hydroxide (0.1 M, 30 mL) and DCM (40 mL). The aqueous phase was extracted with a further two portions of dichloromethane (30 mL) and combined organic layers were dried ($MgSO_4$). The organic residue was purified by column chromatography (4:1 60-80 petroleum ether/ethyl acetate) to give the *title compound* (128 mg, 42%) as colourless oil, which solidified to a white solid on storage in the freezer. Analytical data of **321** agree with literature;[154] R_f 0.29 (4:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 3548, 2947, 1630, 1155; δ_H (360 MHz; $CDCl_3$) 1.63 (2H, dd, J 15.05, 0.62 Hz, 2,4-H), 2.17-2.24 (2H, m, 2,4-H), 3.91 (1H, t, ^3J 5.71 Hz, 3-H), 4.67 (2H, d, ^3J 4.03 Hz, 1,5-H), 6.40 (1H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 36.5 (t, 2,4-C), 65.7 (d, 3-C), 78.0 (d, 1,5-C), 136.2 (d, 6,7-C); *m/z* (EI) 126 (M^+; 60%), 108(47), 68 (100).

(*endo*-3-Dimethylsilanyloxy)-8-oxa-bicyclo[3.2.1]oct-6-ene (322)



A mixture of alcohol **321** (165 mg, 1.30 mmol) and tetramethyldisilazane (2.20 mL, 9.60 mmol) was heated to 75 °C (oil-bath) for 4 h and then cooled to room temperature. The excess silazane was removed in vacuo to give silyl ether **322** (120 mg, 50%) as a light yellow oil that was used in the next step without further purification; υ_{max} (neat)/cm^{-1} 2955, 2205, 1629, 1120, 1042; δ_H (360 MHz; $CDCl_3$) 0.00 (6H, s 10-H), 1.44 (2H, dd, J = 14.9, 0.82 Hz, 2,4-H), 1.99-2.06 (2H, m, 2,4-H), 3.94 (1H, t, J = 5.6 Hz, 3-H), 4.38-4.41 (1H, m, 9-H), 4.53 (2H, d, J = 4.1 Hz, 1,5-H), 6.07 (1H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 0.0 (q, 10-C), 36.6 (t, 2,4-C), 67.2 (d, 3-C), 78.9 (d, 1,5-C), 134.9 (d, 6,7-C); *m/z* (EI) 184 (M^+; 10%), 125 (100), 108 (60), 68 (40).

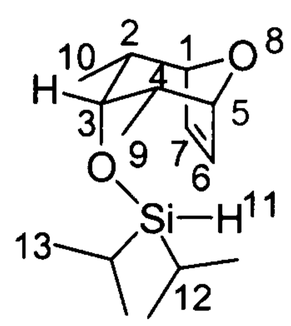
Chlorodiisopropylsilane (324)[156]



To a solution of trichlorosilane (1.50 mL, 14.8 mmol) in diethyl ether (16 mL) maintained at -15 °C (dry ice-EtOH bath) was added dropwise over 30 min isopropylmagnesium chloride (Et_2O, 2 M, 14.8 mL, 29.6 mmol). The mixture was stirred a further 15 min at -15 °C then warmed to room temperature and stirred for 18

h before refluxing for 3 h. The reaction was then filtered and the filtrate concentrated to leave a colourless oil that was distilled under atmospheric pressure to yield pure chlorodiisopropylsilane **324** (730 mg, 33%, lit. 45%); υ_{max} (neat)/cm^{-1} 2959, 2953, 881; δ_H (360 MHz; $CDCl_3$) 1.01-1.05 (12H, m, 3,4-H), 1.50-1.56 (2H, m, 12-H), 4.28 (1H, s, 1-H); δ_C (90 MHz, $CDCl_3$) 13.6 (q, 2-C), 17.5 (q, C), 17.6 (q, C); *m/z* (EI) 133 (40%), 115 (20), 42 (15).

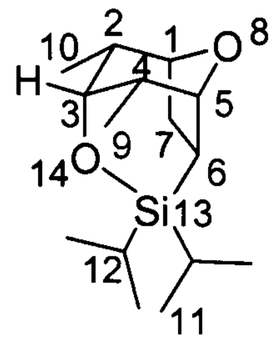
((3-*endo*-Diisopropylsilanyloxy)-2,4-*endo,endo*-dimethyl)-8-oxa-bicyclo[3.2.1]oct-6-ene (325)



A mixture of DMAP (180 μg, 1.5 mmol), triethylamine (640 μL, 4.60 mmol) and alcohol **249** (573 mg, 3.70 mmol) in hexane (20 mL) was stirred at room temperature for 10 min then chlorodiisopropylsilane (730 mg, 4.80 mmol) added dropwise. The mixture was stirred for 4.5 h then filtered through celite, the filtrate was concentrated in vacuo to give an oil that was purified by column chromatography (3:1 60-80 petroleum ether/diethyl ether). Silyl ether **325** was obtained as a colourless oil (390 mg, 55%); R_f 0.50 (3:1 60-80 petroleum ether/diethyl ether); υ_{max} (neat)/cm^{-1} 2964, 1117, 1051, 921; δ_H (360 MHz; $CDCl_3$) 0.93 (6H, d, J = 7.4 Hz, 9,10-H), 1.03 (12H, d, J = 8.3 Hz, 13-H), 1.28 (2H, s, *br*, 12-H), 2.18-2.22 (2H, m, 2,4-H), 4.00 (1H, t, J = 4.4 Hz, 3-H), 4.19 (1H, s, 11-H), 4.40 (2H, d, J = 3.1 Hz, 1,5-H), 6.27 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 13.0 (d, 12-C), 14.2 (q, 9,10-C), 18.0 (q, 13-C), 39.1 (d, 2,4-C),

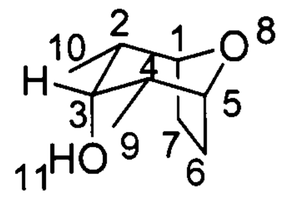
74.1 (d, 3-C), 82.7 (d, 1,5-C), 134.1 (d, 6,7); *m/z* (EI) 268 (100%), 225 (80), 121 (55), 95 (75); HRMS calcd for $C_{15}H_{28}O_2SiNa^+$ 291.0316, found 291.0318.

(±)-(*endo*,*endo*)-4,10-Dimethyl -13-diisopropyl-8,14-dioxa-13-sila-tricyclo[4.3.1.0^{5,6}]decane (326)



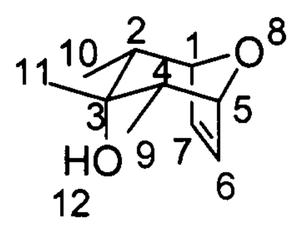
To a mixture of Wilkinson's catalyst (2.5 mg, 0.2 mol%) and 4 Å molecular sieves (7.5 mg) in THF (0.5 mL) was added dropwise a solution of hydrosilane **325** (100 mg, 370 μmol) in THF (0.5 mL) at room temperature. The mixture was refluxed for 4.5 h then cooled to room temperature and concentrated in vacuo. The brown oily residue was purified by column chromatography (5:1 hexane/diethyl ether) to give oxasilacyclohexane **326** (32.7 mg, 33%) as a colourless oil; R_f 0.30 (5:1 hexane/diethyl ether); υ_{max} (neat)/cm^{-1} 2958, 1120, 1048, 918; δ_H (360 MHz; $CDCl_3$) 0.85 (6H, d, J = 7.3 Hz, 9,10-H), 1.03 (12H, d, J = 4.2 Hz, 11-H), 1.28 (2H, *br*, 12-H), 1.93-1.98 (2H, m, 2,4-H), 2.01-2.13 (3H, m, 6,7-H), 3.77 (1H, t, J = 4.7 Hz, 3-H), 3.90-3.93 (2H, m, 1,5-H); δ_C (90 MHz, $CDCl_3$) 13.0 (d, 12-C), 13.4 (d, 6-C), 14.2 (q, 9,10-C), 18.1 (q, 11-C), 25.0 (t, 7-C), 40.7 (d, 2,4-C), 74.8 (d, 3-C), 78.9 (d, 1,5-C); *m/z* (EI) 268 (100%), 225 (73), 147 (55); HRMS calcd for $C_{15}H_{28}O_2SiNa^+$ 291.1123, found 291.1119.

(*endo*,*endo*)-2,4-Dimethyl-8-oxa-bicyclo[3.2.1]octan-(*endo*)-3-ol (327)

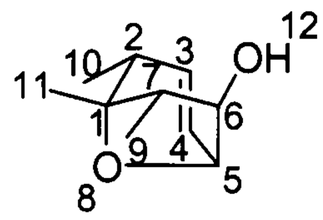


TBAF in THF (450 μL, 1.0 M, 450 μmol) was added to a solution of **326** (30.0 mg, 110 μmol) in THF (0.6 mL) at room temperature. The mixture was brought to reflux, and heating continued for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined ethereal layer was dried ($MgSO_4$) and concentrated under atmospheric pressure. The organic residue was purified by column chromatography (5:1 60-80/ethyl acetate) to give compound **327** (10 mg, 57%) as a pale yellow oil. Analytical data agree with literature;[152] R_f 0.37 (5:1 60-80/ethyl acetate); υ_{max} (neat)/cm^{-1} 3518, 2944, 1119, 1049; δ_H (360 MHz; $CDCl_3$) 0.90 (6H, d, J = 7.3 Hz, 9,10-H), 1.20 (1H, s, *br*, 11-H), 1.61-1.66 (2H, m, 6,7-H), 1.92-2.00 (2H, m, 6,7-H), 3.62 (2H, t, J = 3.9 Hz, 3-H), 3.96 (2H, dd, J = 6.9 and 3.6 Hz, 1,5-H); δ_C (90 MHz, $CDCl_3$) 13.4 (q, 9,10-C), 25.0 (t, 6,7-C), 39.5 (d, 2,4-C), 72.4 (d, 3-C), 78.5 (d, 1,5-C); *m/z* (EI) 156 (M^+; 100%), 138 (78), 68 (45).

(*endo*-2-*exo*-3-*endo* 4-)-Trimethyl-8-oxa-bicyclo[3.2.1]oct-6-en-(*endo*)-3-ol (331) and (±)-(*exo*-1–*endo*,*endo*-2,7)-Trimethyl-8-oxa-bicyclo[3.2.1]oct-3-en-(*exo*)-6-ol (332)



331



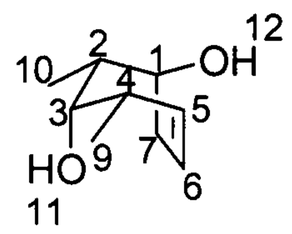
332

To a solution of ketone **243** (957 mg, 6.21 mmol) in THF (20 mL) was added MeLi (Et_2O, 0.9 M, 14 mL, 12.6 mmol) at -78 °C. The reaction was stirred for 30 min at -78 °C and then allowed to warm to 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by column chromatography (2:1 60-80 petroleum ether/ethyl acetate) to give first compound **331** (530 mg, 51%), followed by compound **332** (193 mg, 18%). Analytical data for **331**; R_f 0.46 (2:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm $^{-1}$ 3526, 2957, 1119, 1044; δ_H (360 MHz; $CDCl_3$) 0.84 (6H, d, J = 7.3 Hz, 9,10-H), 1.01 (1H, d, J = 0.7 Hz, 11-H), 1.63 (1H, s, 12-H), 1.96-2.19 (2H, m, 2,4-H), 4.41 (2H, d, J = 3.6 Hz, 1,5-H), 6.48 (2H, s, 6,7-H); δ_C (90 MHz, $CDCl_3$) 10.9 (q, 9,10-C), 27.4 (q, 11-C), 42.8 (d, 2,4-C), 73.6 (s, 3-C), 83.3 (d, 1,5-C), 135.8 (d, 6,7); *m/z* (EI) 168 (M^+; 74%), 97 (100), 72 (87).

Analytical data for **332**; R_f 0.29 (2:1 60-80 petroleum ether/ethyl acetate); υ_{max} (neat)/cm^{-1} 3518, 2963, 1124, 1051; δ_H (360 MHz; $CDCl_3$) 1.04 (3H, d, J = 7.0 Hz, 9-H), 1.12 (6H, t, J = 7.2 Hz, 10,11-H), 1.69 (1H, s, 12-H), 1.72-1.78 (2H, m, 7-H), 1.81-1.88 (1H, m, 2-H), 3.87-3.93 (1H, m, 6-H), 4.22 (1H, dd, J = 5.5 and 4.5 Hz, 5-

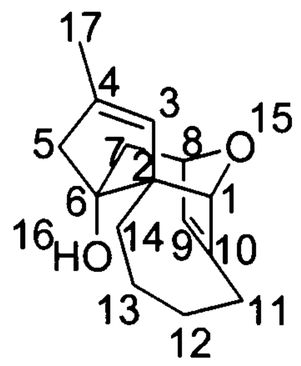
H), 5.83 (1H, dd, J = 9.8 and 4.2 Hz, 4-H), 5.92-5.99 (1H, m, 3-H); δ_C (90 MHz, $CDCl_3$) 15.0 (q), 16.4 (q), 19.8 (q), 44.0 (d), 49.0 (d), 74.2 (d, 6-C), 82.5 (s, 1-C), 86.7 (d, 5-C), 127.0 (d), 135.8 (d); *m/z* (EI) 168 (M^+; 30%), 95 (100), 83 (65); HRMS calcd for $C_{10}H_{16}O_2Na^+$ 191.2335, found 191.2330.

(±)-2,4-Dimethyl-cyclohept-5-ene-1-3-diol (342)



Red-Al (toluene, 70% w/w, 2.2 ml, 8.13 mmol) was added dropwise to a solution of alcohol **249** (313 mg, 2.03 mmol) in toluene (2.5 mL) at room temperature. The mixture was brought to reflux for 24 h and then cooled before water and concentrated H_2SO_4 were added. The aqueous phase was extracted with diethyl ether and the combined ethereal layer was dried ($MgSO_4$) and concentrated. The organic residue was purified by column chromatography (2:1 ethyl acetate/60-80 petroleum ether) to give diol **342** (162 mg, 52%); R_f 0.54 (2:1 ethyl acetate/60-80 petroleum ether); υ_{max} (neat)/cm $^{-1}$ 3439 (*br*), 2953, 1055; δ_H (360 MHz; $CDCl_3$) 1.20 (3H, d, J = 2.2 Hz, 9-H), 1.23 (2H, d, J = 2.7 Hz, 10-H), 1.26 (1H, s, 12-H), 1.61 (1H, s, 11-H), 1.69-1.74 (1H, m, 2-H), 2.38-2.42 (2H, m, 7-H), 2.60-2.66 (1H, m, 4-H), 3.39-3.44 (1H, m, 3-H), 3.50 (1H, d, J = 7.2 Hz, 1-H), 5.30-5.39 (1H, m, 5-H), 5.80-5.94 (1H, m, 6-H); δ_C (90 MHz, $CDCl_3$) 17.9 (q), 20.7 (q), 38.0 (t, 7-C), 38.8 (d, 4-C), 50.2 (d, 2-C), 69.2 (d), 78.7 (d), 129.0 (d), 135.7 (d); *m/z* (EI) 156 (M^+; 21%), 138 (55), 68 (100); HRMS calcd for $C_9H_{16}O_2Na^+$ 179.0571, found 179.0567.

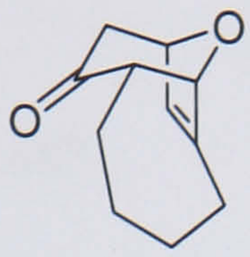
(±)-4-Methyl-15-oxa-tetracyclo[10.2.1.$0^{2,6}$]pentadeca-3,9-dien-(*endo*)-6-ol (343)

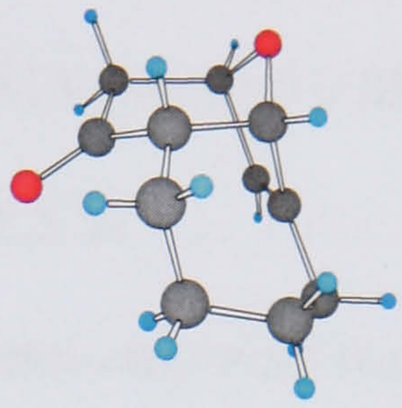


TBAF in THF (0.06 μL, 1.0 M, 1.20 mmol) was added to a solution of **296** (15.2 mg, 50 μmol), in THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature over 3 h. The reaction was quenched with aqueous NH_4Cl (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined ethereal layer was dried ($MgSO_4$) and concentrated under atmospheric pressure. The organic residue was purified by column chromatography (4:1 hexane/ethyl acetate) to give the title compound (11.2 mg, 97%) as a colourless oil; R_f 0.24 (4:1 hexane/ethyl acetate); υ_{max} (neat)/cm^{-1} 3543, 3050, 2960, 1642, 1124; δ_H (360 MHz; $CDCl_3$) 1.04-1.10 (1H, m, 14-H), 1.30-1.39 (1H, m, 14-H), 1.58-1.75 (7H, m, 12,13,17- H), 1.77-1.82 (1H, m, 7-H), 1.84-1.88 (1H, m, 7-H), 1.95 (1H, s, *br*, 16-H), 2.01 (1H, dd, J = 14.5 and 3.9 Hz, 5-H), 2.39-2.44 (2H, m, 11-H), 2.51 (1H, d, J = 15.3 Hz, 5-H), 4.40 (1H, s, 1-H), 4.53-4.58 (1H, m, 8-H), 5.18 (1H, q, J = 1.8 Hz, 9-H), 5.84 (1H, q, J = 1.8 Hz, 3-H), δ_C (90 MHz, $CDCl_3$) 17.7 (q, 17-C), 26.21 (t, C), 26.9 (t, C), 28.0 (t, C), 34.9 (t, C), 41.4 (t, C), 51.0 (s, 2-C), 55.0 (t, C), 78.1 (d, 8-C), 81.6 (s, 6-C), 83.1 (d, 1-C), 125.8 (d, 9-C), 133.9 (d, 3-C), 136.0 (s, 4-C), 150.1 (s, 10-C); *m/z* (EI) 232 (M^+; 100%), 190 (30), 143 (45); HRMS calcd for $C_{15}H_{20}O_2Na^+$ 255.1355, found 255.1357.

CHAPTER 6

X-ray data for compound 195





crystal structure of **195** from X-ray coordinates

Table 1. Crystal data and structure refinement for **195**.

Identification code	C:aA.CIF	
Empirical formula	$C_{11} H_{14} O_2$	
Formula weight	178.22	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 22.1341(6) Å	a= 90°.
	b = 7.6802(3) Å	b= 107.876(2)°.
	c = 11.0101(3) Å	g = 90°.
Volume	1781.30(10) $Å^3$	
Z	8	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	768	
Crystal size	0.80 x 0.80 x 0.30 mm^3	

Theta range for data collection	3.59 to 27.48°.
Index ranges	-28<=h<=28, -8<=k<=9, -14<=l<=14
Reflections collected	2933
Independent reflections	1813 [R(int) = 0.0505]
Completeness to theta = 27.48°	88.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9735 and 0.9315
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1813 / 0 / 119
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.0971
R indices (all data)	R1 = 0.0500, wR2 = 0.1031
Extinction coefficient	0.021(3)
Largest diff. peak and hole	0.275 and -0.244 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x10^3) for **195**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	681(1)	3332(1)	11036(1)	22(1)
C(1)	965(1)	1712(2)	10860(1)	17(1)
O(2)	800(1)	2201(1)	7542(1)	21(1)
C(2)	643(1)	1114(2)	9467(1)	15(1)
C(3)	718(1)	2541(2)	8562(1)	15(1)

C(4)	671(1)	4405(2)	8975(1)	20(1)
C(5)	984(1)	4565(2)	10427(1)	22(1)
C(6)	1656(1)	3895(2)	10776(1)	22(1)
C(7)	1652(1)	2206(2)	11033(1)	19(1)
C(8)	2179(1)	896(2)	11325(1)	25(1)
C(9)	1967(1)	-923(2)	10788(1)	26(1)
C(10)	1558(1)	-948(2)	9376(1)	21(1)
C(11)	845(1)	-691(2)	9161(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for **195**.

O(1)-C(1)	1.4341(15)
O(1)-C(5)	1.4403(17)
C(1)-C(7)	1.5222(18)
C(1)-C(2)	1.5483(17)
O(2)-C(3)	1.2191(15)
C(2)-C(3)	1.5240(17)
C(2)-C(11)	1.5260(18)
C(3)-C(4)	1.5152(18)
C(4)-C(5)	1.5406(18)
C(5)-C(6)	1.5072(19)
C(6)-C(7)	1.328(2)
C(7)-C(8)	1.4986(19)
C(8)-C(9)	1.533(2)
C(9)-C(10)	1.5397(18)

C(10)-C(11)	1.5347(18)
C(1)-O(1)-C(5)	102.76(9)
O(1)-C(1)-C(7)	103.28(10)
O(1)-C(1)-C(2)	107.67(10)
C(7)-C(1)-C(2)	109.65(10)
C(3)-C(2)-C(11)	114.23(10)
C(3)-C(2)-C(1)	108.99(10)
C(11)-C(2)-C(1)	114.28(10)
O(2)-C(3)-C(4)	121.47(12)
O(2)-C(3)-C(2)	121.67(12)
C(4)-C(3)-C(2)	116.84(10)
C(3)-C(4)-C(5)	109.67(11)
O(1)-C(5)-C(6)	102.77(11)
O(1)-C(5)-C(4)	107.73(11)
C(6)-C(5)-C(4)	109.39(10)
C(7)-C(6)-C(5)	108.56(12)
C(6)-C(7)-C(8)	130.28(13)
C(6)-C(7)-C(1)	106.73(12)
C(8)-C(7)-C(1)	122.78(12)
C(7)-C(8)-C(9)	113.77(11)
C(8)-C(9)-C(10)	114.59(11)
C(11)-C(10)-C(9)	114.34(11)
C(2)-C(11)-C(10)	116.10(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **195**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	17(1)	21(1)	-1(1)	15(1)	5(1)
C(1)	24(1)	14(1)	15(1)	1(1)	9(1)	4(1)
O(2)	27(1)	21(1)	15(1)	1(1)	9(1)	0(1)
C(2)	16(1)	14(1)	16(1)	1(1)	6(1)	0(1)
C(3)	12(1)	18(1)	15(1)	1(1)	3(1)	1(1)
C(4)	26(1)	15(1)	20(1)	3(1)	8(1)	2(1)
C(5)	33(1)	13(1)	21(1)	-2(1)	11(1)	0(1)
C(6)	25(1)	24(1)	17(1)	-5(1)	4(1)	-6(1)
C(7)	23(1)	24(1)	10(1)	-2(1)	3(1)	0(1)
C(8)	21(1)	33(1)	20(1)	2(1)	2(1)	5(1)
C(9)	26(1)	26(1)	25(1)	6(1)	8(1)	12(1)
C(10)	25(1)	18(1)	24(1)	-1(1)	11(1)	6(1)
C(11)	23(1)	14(1)	19(1)	1(1)	9(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **195**.

	x	y	z	U(eq)
H(1)	930	813	11491	20
H(2)	179	1036	9359	18
H(4A)	219	4754	8748	24
H(4B)	886	5190	8525	24
H(5)	964	5780	10739	26
H(6)	2021	4567	10808	27
H(8A)	2369	808	12263	30
H(8B)	2513	1316	10971	30
H(9A)	1722	-1467	11304	31
H(9B)	2349	-1646	10884	31
H(10A)	1709	-18	8918	26
H(10B)	1622	-2076	8998	26
H(11A)	616	-953	8256	22
H(11B)	706	-1553	9688	22

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CHAPTER 8

Publications

(Please turn over for publications)

JOC*Note*

A Synthetic Alternative to the Type-II Intramolecular 4 + 3 Cycloaddition Reaction

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Abstract: Oxyallyl cations generated in situ from dihaloketones have been found to undergo the Favorskii rearrangement in preference to an intramolecular Type-II 4 + 3 cycloaddition reaction in trifluoroethanol and hexafluoropropan-2-ol solvents, generating acrylate esters with high cis selectivity. A synthetic alternative to the intramolecular Type-II 4 + 3 cycloaddition has been developed on the basis of intramolecular enolate alkylation to close a 7-membered ring with an exocyclic double bond.

The 4 + 3 cycloaddition reaction between a diene and an allylic cation is a powerful method for the synthesis of 7-membered rings.[1] In the intramolecular series, Harmata has delineated six possible ways of linking the diene with the allylic cation (Figure 1).[2] To date, only examples of the Type-I system have been reported in the literature.

As part of a synthetic approach to the diterpene ingenol, we have investigated the Type-II intramolecular 4 + 3 cycloaddition reaction of an oxyallyl cation tethered to the 3-position of a furan as a means to construct the [4.4.1] bicyclic skeleton (BC ring system) of the natural product (Scheme 1).[3] We envisage that stereoselective reduction of the bridgehead double bond system **1** offers a means to access the thermodynamically unfavorable trans ring junction (in−out stereochemistry)[4] deemed essential for the biological activity of ingenol.[5,6] Here, we report our attempts to achieve such a transformation, the problems associated with such an approach, and an alternative, more successful method for the construction of the desired ring system **1** based on intramolecular enolate alkylation.

In general, oxyallyl cations are too unstable to be isolated and are typically generated in situ. Although a variety of precursors can be used to generate oxyallyl cations, α-haloketones have found most application in the chemical literature.[1,2] Construction of α-dihaloketones **5** and **6** required to test the proposed Type-II cyclization are shown in Scheme 2. Homologation of 3-furfuryl alcohol **2**[7] was carried out via a known three-step sequence.[8] Conversion of alcohol **3** to the corresponding bromide followed by displacement with dimethylmalonate and Krapcho decarboxylation gave monoester **4**, which could be converted into the dichloroketone **5** or dibromoketone **6** using Barluenga's methodology.[9]

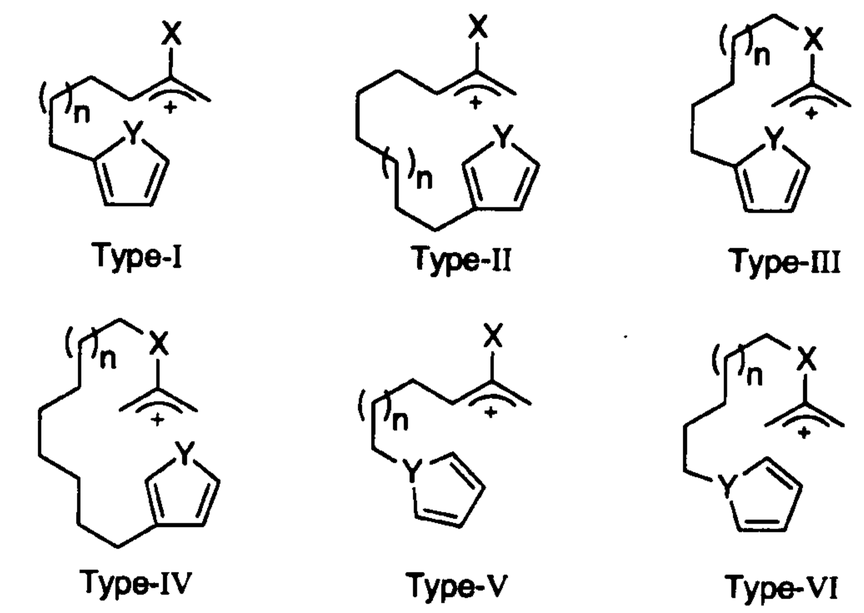
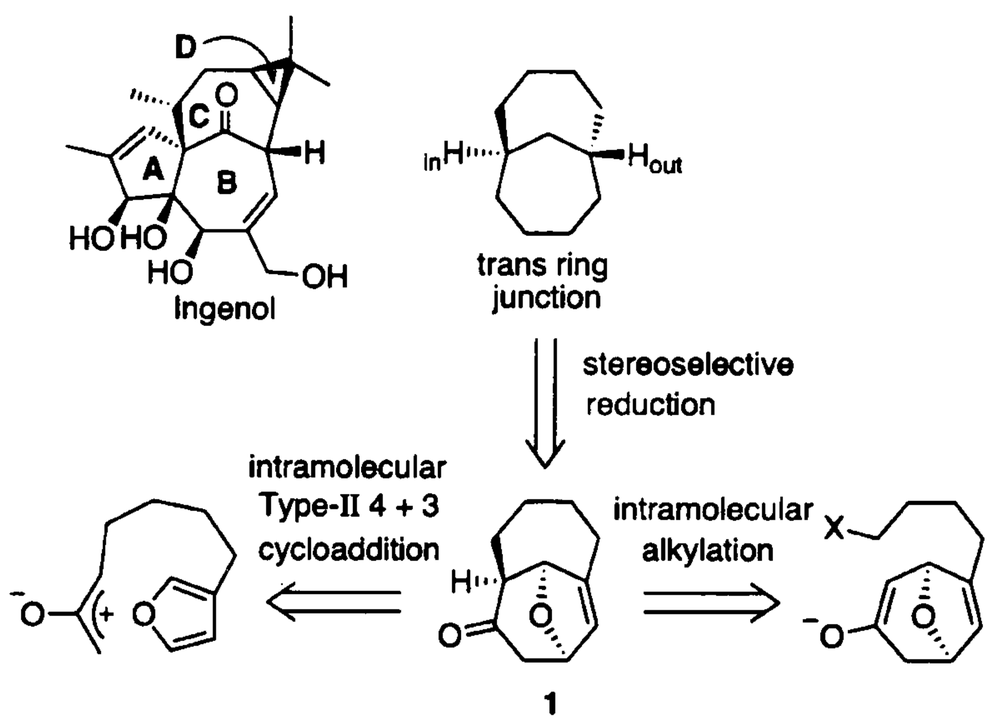


FIGURE 1. Intramolecular 4 + 3 cycloaddition reactions of allylic cations.

SCHEME 1



† To whom correspondence regarding the X-ray crystal structure should be addressed.

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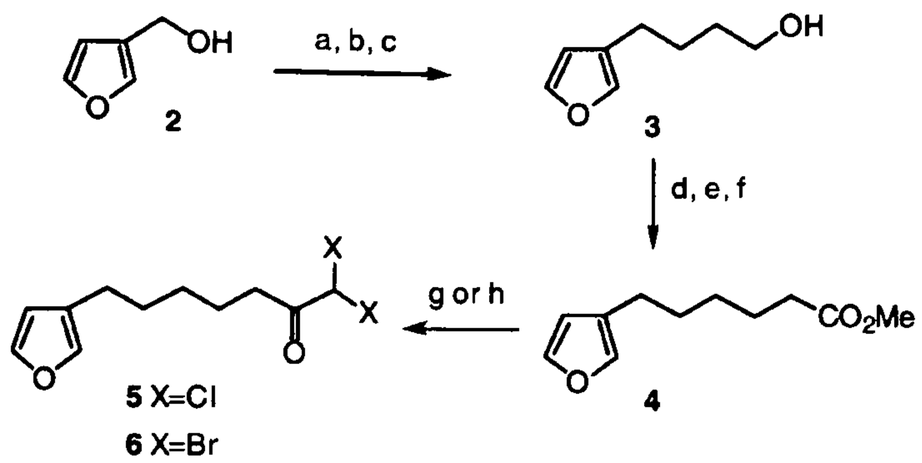
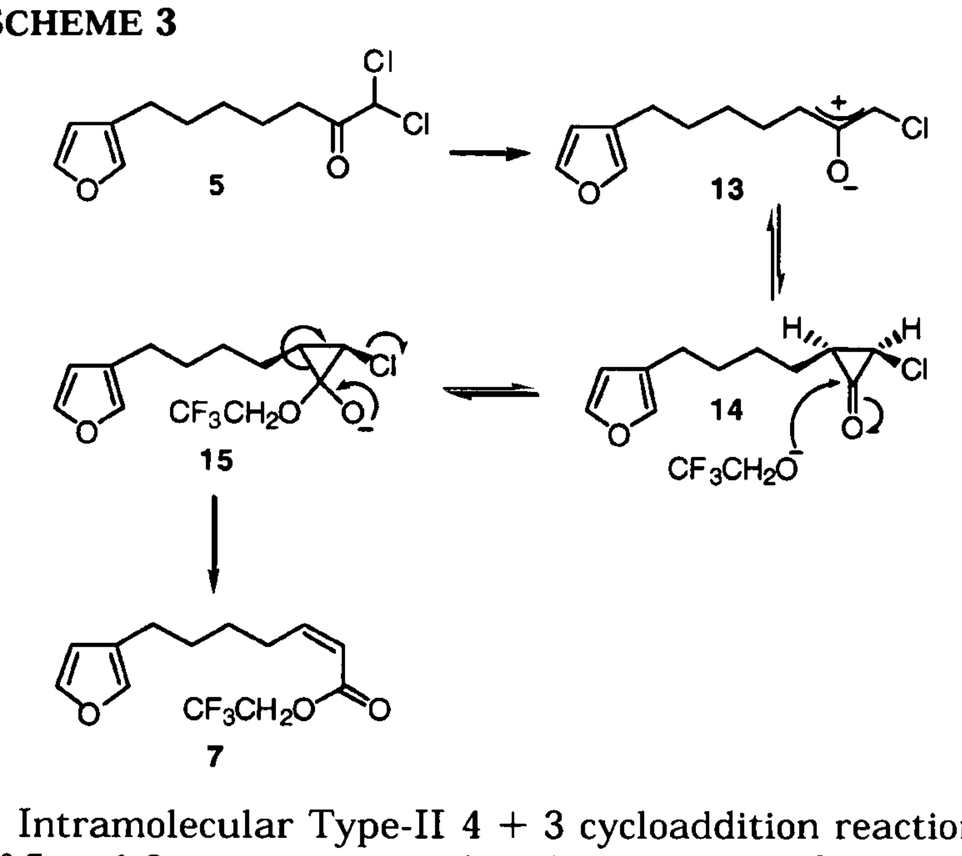
SCHEME 2[a]



[a] Reagents and conditions: (a) PBr_3, pyridine, Et_2O; (b) allylMgCl, THF; (c) Sia_2BH, then NaOH, H_2O_2, 45% over three steps; (d) CBr_4, Ph_3P, CH_2Cl_2, rt, 3 h, 89%; (e) dimethyl malonate, NaH, DMF, THF, reflux, 24 h, 70%; (f) NaCl, DMSO, H_2O, reflux, 3 h, 90%; (g) Cy_2NLi, CH_2Cl_2, THF, −78 °C, 2 h, 64% **5**; (h) LDA, CH_2Br_2, THF, −78 °C, 2 h, 63% **6**.

SCHEME 3



Intramolecular Type-II 4 + 3 cycloaddition reactions of **5** and **6** were attempted under a variety of standard conditions, including $LiClO_4/Et_3N/Et_2O$, Et_3N/trifluoroethanol (TFE), and NaTFE/TFE.[10] Reactions proceeded slowly at room temperature to give complex mixtures of products. Analysis of ^1H NMR of the crude reaction mixtures suggested retention of the monosubstituted furan functionality under almost all conditions.[11] In the case of reactions in trifluoroethanol, slow conversion to a mixture of trifluoroethyl acrylic esters **7** and **8** was observed, the ratio of which varied with the base used to generate the oxyallyl cation (Table 1, entries 1−3).

The formation of **7** and **8** can be ascribed to a competing Favorskii rearrangement in preference to the desired 4 + 3 cycloaddition reaction (Scheme 3). The cis double-bond geometry in **7** was assigned on the basis of coupling constants in the ^1H NMR spectrum and is consistent with a stereospecific disrotative ring closure of an oxyallyl cation **13** to a *cis*-cyclopropane **14**, followed by a stereospecific S_N2-type ring opening via **15** to **7**.[12] The formation of the 2-methylene ester **8** can be ascribed to elimination of an α-chloromethyl ester formed via opening of the alternative C−C bond in the cyclopropane intermediate **15** or via Favorskii rearrangement of a 1,3-dichloroketone formed via 1,3-Cl migration in **5**.

Products derived from Favorskii rearrangements have been observed as minor components in 4 + 3 cycloaddition reactions of oxyallyl cations,[13] but their formation is generally minimized by the use of the nonnucleophilic solvent, trifluoroethanol. Recourse to the even less nucleophilic solvent hexafluoropropan-2-ol suppressed the Favorskii rearrangement of dichloroketone **5** and promoted formation of the desired cycloadduct **9** (albeit in low yield), thus establishing for the first time that the Type-II 4 + 3 cyclization mode is possible (Table 1, entries 4 and 5). Unfortunately, application of these conditions to the dibromoketone **6** only gave trace amounts of the desired cycloadduct **11**, with *cis*-alkene **10** now predominating (Table 1, entry 6).

The results in Table 1 clearly demonstrate that although the Type-II cyclization mode is possible, it is never going to be synthetically viable under these reaction conditions. Although a range of alternative substrates for oxyallyl cation formation can be envisaged which might avoid the problem of competing Favorskii rearrangement,[14] we chose instead to investigate a complementary approach to the requisite ring system **1**, involving a novel intramolecular enolate alkylation to close a 7-membered ring (Scheme 1).[15] Analysis of simple molecular models suggested the conformation required for an intramolecular S_N2 reaction to occur is only accessible on the face of the enolate opposite the oxygen bridge. Furthermore, cyclization of the desired enolate appeared to be clearly favored over its regioisomer, thereby allowing us to potentially exploit thermodynamic conditions for enolate generation. This strategy was brought into practice as follows (Scheme 4). Intermolecular 4 + 3 cycloaddition of 3-substituted furan **3** with the oxyallyl cation generated in situ from 1,1,3-trichloropropan-2-one proceeded readily to provide alcohol **16** after dehalogenation. A variety of bases (KH, NaH, LDA, KHMDS, Cs_2CO_3, KO-*t*-Bu) and conditions (solvent/temperature) have been screened for the 7-membered ring closure on both tosylate **17** and bromide **18**. Potassium *tert*-butoxide proved greatly superior to other bases—in refluxing THF under high dilution conditions tosylate **17** can be closed to ketone **1** in a synthetically useful 80% yield. Notably, this reaction proceeds without cleavage of the strained ether bridge in **1**.[16] The structure of **1** has been unambiguously proven by X-ray crystallography.[17]

In conclusion, an investigation into a Type-II intramolecular 4 + 3 cycloaddition has shown the Favorskii

(10) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Henle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem.* **1999**, *64*, 3398.

(11) Disubstituted furans can potentially arise via an intramolecular aromatic substitution reaction. For a recent example, see: Kreiselmeier, G.; Föhlisch, B. *Tetrahedron Lett.* **2000**, *41*, 1375.

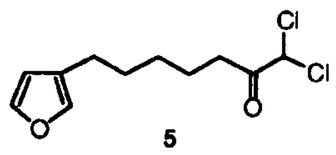
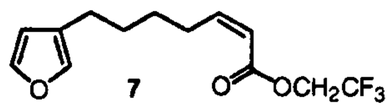
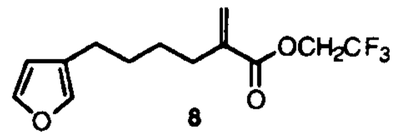
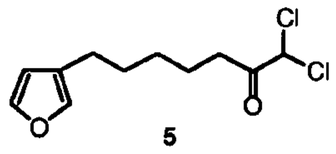
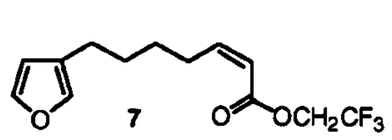
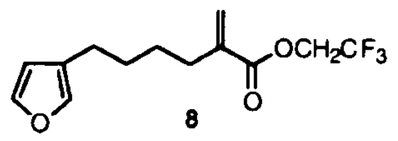
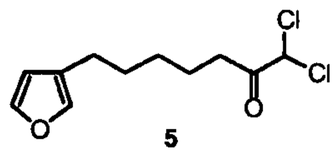
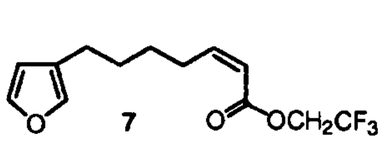
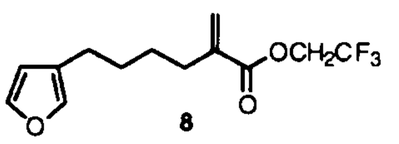
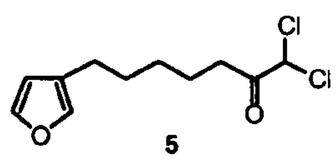
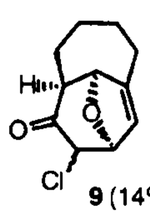
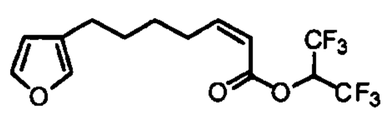
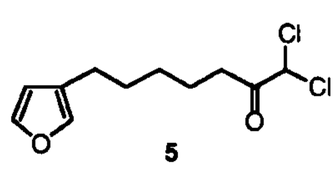
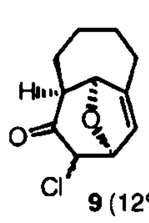
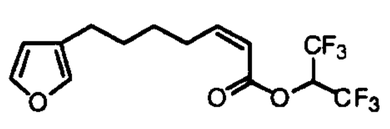
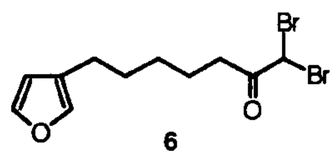
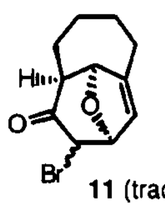
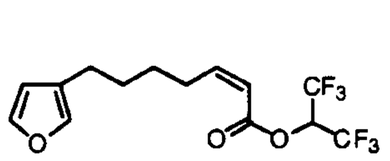
(12) Schamp, N.; De Kimpe, N.; Coppens, W. *Tetrahedron* **1975**, *31*, 2081.

(13) (a) Föhlisch, B.; Gehrlach, E.; Henle, G.; Boberlin, U.; Gekeler, M.; Geywitz, B.; Ruck, M.; Vogl, H. *J. Chem. Res., Miniprint* **1991**, 1401. (b) Reference 11. (c) Föhlisch, B.; Kreiselmeier, G. *Tetrahedron* **2001**, *57*, 10077.

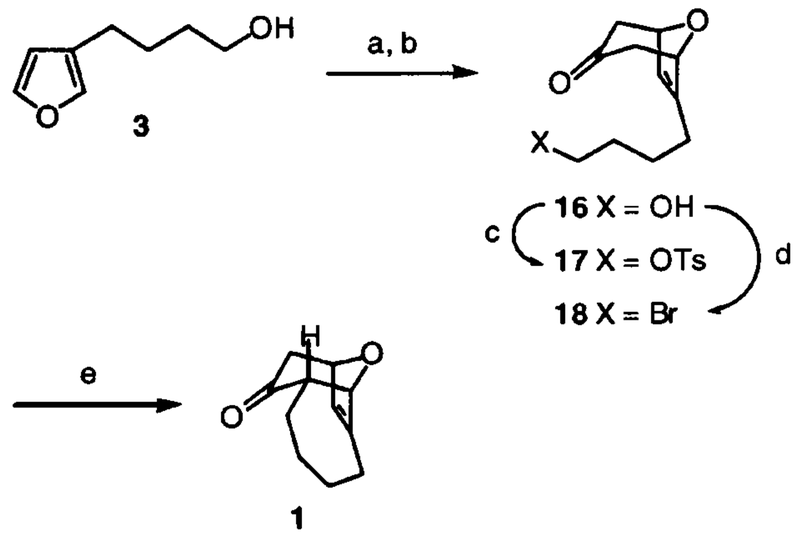
(14) For recent examples, see: (a) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425. (b) Cho, S. Y.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2891. (c) Aungst, R. A., Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553. (d) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (e) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595 and references therein. (f) Handy, S. T.; Okello, M. *Synlett* **2002**, 489. (g) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

(15) For representative examples of 7-membered ring-closure via enolate alkylation, see: (a) Conia, J.-M.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1963**, 1930. (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051. (c) Spreitzer, H.; Pichler, A.; Holzer, W.; Schlager, C. *Helv. Chim. Acta* **1998**, *81*, 40.

TABLE 1. Attempted Type-II Intramolecular 4 + 3 Cycloaddition Reactions of Dihaloketones 5 and 6

entry	dihaloketone	conditions	products (isolated yield)
1	 **5**	Et_3N (2.2 eq.), CF_3CH_2OH (0.17M), rt, 7 days	 **7**  **8** 4 : 1 (62%)
2	 **5**	Et_3N (2.2 eq.), CF_3CH_2OH (0.8M), 50°C, 24h	 **7**  **8** 4 : 1 (57%)
3	 **5**	$NaOCH_2CF_3$, CF_3CH_2OH, (0.8M), rt, 5days	 **7**  **8** 1 : 1 (65%)
4	 **5**	Et_3N (2.2 eq.), $(CF_3)_2CHOH$ (0.8M), rt, 7 days	 **9** (14%)  **10** (trace)
5	 **5**	$NaOCH(CF_3)_2$, $(CF_3)_2CHOH$ (0.8M), rt, 5 days	 **9** (12%)  **10** (3%)
6	 **6**	Et_3N (2.2 eq.), $(CF_3)_2CHOH$ (0.8M), rt, 7 days	 **11** (trace)  **10** (65%)

SCHEME 4[a]



[a] Reagents and conditions: (a) 1,1,3-trichloropropan-2-one, $NaOCH_2CF_3$, CF_3CH_2OH, rt, 3 days; (b) Zn, CuBr, MeOH, 2 days, 54% over two steps; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 4.5 h, 64%; (d) CBr_4, Ph_3P, CH_2Cl_2, 71%; (e) *t*-BuOK, THF, reflux, 80% from **17**, 60% from **18**.

rearrangement to be the major reaction pathway for oxyallyl cations generated from dihaloketones under classical conditions.[18] The low yields of the Type-II cycloadduct have necessitated the development of an alternative approach to the same ring system based on intramolecular enolate alkylation under thermodynamic conditions. Further studies on the selective functionalization and ring opening of oxatricyclic systems such as **1** are in progress and will be reported in due course.

Experimental Section

Intermolecular 4 + 3 Cycloaddition of Furan (3). A solution of $NaOCH_2CF_3$ (10.7 mL, 21.4 mmol) in CF_3CH_2OH (10.7 mL) and 1,3,3-trichloroacetone (2.3 mL, 2.4 mmol) were added separately via syringe to alcohol **3** (1.5 g, 10.7 mmol) over 1 h at 0 °C. The reaction was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched with water and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated to give a crude product that was taken up in methanol (10 mL) and added to a solution of Zn (14.8 g, 227.3 mmol) and Cu(I)Br (8.7 g, 60.6 mmol) in methanol (130 mL). The mixture was stirred at room temperature for 2 days before filtering through 10 g of Celite and the filtrate concentrated to give a residue the was dissolved in a 5% solution of HCl. The aqueous layer was extracted with diethyl

(16) Reviews on ring opening: (a) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669. (b) Chiu, P.; Lautens, M. In *Topics in Current Chemistry, Vol. 190*; Metz, P., Ed.; Springer-Verlag: New York, 1997; pp 1−85. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(17) The author has deposited X-ray coordinates with the Cambridge Crystallographic Data Center (CCDC 202411).

(18) Although determination of the optimal chain length between diene and oxyallyl cation was not the aim of this study, it may well be that other systems undergo the Type-II 4 + 3 cycloaddition with greater ease than **5** or **6**. In this respect, it is perhaps notable that to the best of our knowledge Type-I intramolecular 4 + 3 cycloadditions are only known with three or four atoms in the tether to form five- or six-membered rings, respectively.

ether and once with ethyl acetate. The combined organic layer was dried ($MgSO_4$) and concentrated a crude residue that was purified by column chromatography (3:1 60−80 petroleum ether/ethyl acetate) to give **16** (807 mg, 54% over two steps) as a light yellow oil: R_f 0.23 (3:1 ethyl acetate/60−80 petroleum ether); ν_{max} (neat) 3430 br, 2940, 1708 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.52 (m, 4 H), 1.82 (br, 1 H), 2.08 (br, 2 H), 2.27 (m, 2 H), 2.62 (m, 2 H), 3.57 (t, J = 5.3 Hz, 2 H), 4.72 (d, J = 4.9 Hz, 1 H), 4.92 (d, J = 4.5 Hz, 1 H), 5.76 (d, J = 1.6 Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 23.9 (CH_2), 27.3 (CH_2), 32.6 (CH_2), 46.5 (CH_2), 46.6 (CH_2), 62.9 (CH_2), 78.0 (CH), 80.0 (CH), 126.1 (CH), 148.0 (C), 206.4 (C); *m/z* (EI) 196 (M^+; 97.3), 178 (43), 153 (92), 95 (100); HRMS calcd for $C_{11}H_{16}O_3Na$ (M + Na^+) 219.0992, found 219.0989.

Bromide (18). To a solution of alcohol **16** (1.0 g, 5.1 mmol) and carbon tetrabromide (2.1 g, 6.3 mmol) in CH_2Cl_2 (30 mL) was added portionwise triphenylphosphine (2.1 g, 8.0 mmol) at 0 °C. The mixture was stirred for 2 h while warming to room temperature. The reaction was quenched with water, followed by extraction with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration of the organic layer in vacuo gave a residue that was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to afford the title compound (940 mg, 71%) as a colorless oil: R_f 0.45 (3:2 petroleum ether/ethyl acetate); ν_{max} (neat) 2939, 1711 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.66 (m, 2 H), 1.89 (m, 2 H), 2.15 (m, 2 H), 2.35 (m, 2 H), 2.75 (m, 2 H), 3.42 (t, J = 6.6 Hz, 2 H), 4.79 (d, J = 4.9 Hz, 1 H), 5.00 (d, J = 4.5 Hz, 1 H), 5.85 (d, J = 3.5 Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 26.09 (CH_2), 26.6 (CH_2), 32.5 (CH_2), 33.8 (CH_2), 46.5 (CH_2), 78.0 (CH), 79.4 (CH), 126.3 (CH), 148.0 (C), 206.1 (C); *m/z* (EI) 258 (M^+; 36.7), 217 (100), 279 (35), 137 (59); HRMS calcd for $C_{11}H_{15}O_2BrNa$ (M + Na^+) 281.0148, found 281.0111.

Tosylate (17). To a suspension of alcohol **16** (200.0 mg, 1.02 mmol), 4-DMAP (11.0 mg, 0.09 mmol), and triethylamine (0.63 mL, 4.52 mmol) in CH_2Cl_2 (11 mL) was added *p*-toluenesulfonyl chloride (328 mg, 1.72 mmol) in one portion with cooling in an ice−water bath. The reaction was stirred for 4.5 h while warming to room temperature and then diluted with diethyl ether (15 mL). The organic phase was washed with aqueous sodium bicarbonate solution and dried ($MgSO_4$). The crude reaction was purified by column chromatography (2:1 petroleum ether 60−80/ethyl acetate) to give **17** (227 mg, 64%): mp 42−43 °C; R_f 0.48 (2:1 60−80 petroleum ether/ethyl acetate); ν_{max} (neat) 2930, 2360, 1700, 1050 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.51 (m, 4 H), 1.99 (m, 2 H), 2.23 (m, 2 H), 2.39 (s, 3 H), 2.66 (m, 2 H), 3.96 (t, J = 6.1 Hz, 2 H), 4.67 (d, J = 4.9 Hz, 1 H), 4.90 (d, J = 4.5 Hz, 1 H), 5.71 (d, J = 1.8 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H); δ_C (90 MHz, $CDCl_3$) 22.1 (CH_3), 23.6 (CH_2), 26.8 (CH_2), 28.8 (CH_2), 46.5 (CH_2), 70.4 (CH_2), 78.0 (CH), 79.4 (CH), 126.3 (C), 128.3 (CH), 130.3 (CH), 133.4 (C), 145 (C), 147.8 (C), 206.0 (C); *m/z* (EI) 350 (M^+; 100), 178 (22), 135 (67), 121 (18); HRMS calcd for $C_{14}H_{14}O_3F_6S$ 350.1188, found 350.1172.

Oxatricyclic Ketone (1). To a stirred solution of KO-*t*-Bu (50 mg, 0.45 mmol) in THF (38 mL) was added a solution of **17** (120 mg, 0.34 mmol) in THF (110 mL). The mixture was refluxed for 1 h, and then a further 1.3 equiv of KO^{t}Bu (50 mg, 0.45 mmol) was added in one portion. The resulting mixture was refluxed for 30 min, by which time the reaction was seen to have gone to completion (by TLC). The reaction was quenched with saturated aqueous NH_4Cl, followed by extraction of the aqueous layer with diethyl ether. The ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to afford compound **1** (47 mg, 80%) as a yellow solid: mp 72−73 °C; R_f 0.42 (3:1 60−80 petroleum ether/ethyl acetate); ν_{max} (neat) 2932, 2858, 1704, 1046 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.14 (m, 4 H), 1.50 (m, 2 H), 1.70 (m, 2 H), 2.15 (m, 1 H), 2.26 (m, 2 H), 2.56 (dd, J = 15.8, 4.6 Hz, 1 H), 2.74 (m, 1 H), 4.72 (d, J = 4.4 Hz, 1 H), 4.97 (t, J = 1.6 Hz, 1 H), 5.64 (s, 1 H); δ_C (90 MHz, $CDCl_3$) 23.7 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 38.1 (CH_2), 46.27 (CH_2), 56.2 (CH), 78.9 (CH), 82.4 (CH), 126.9 (CH), 147.5 (CH), 207.6 (C); *m/z* (EI) 178 (M^+; 100), 149 (24), 121 (41), 79 (27); HRMS calcd for $C_{11}H_{14}O_2$ 179.1072, found 179.1073.

Acknowledgment. We thank EPSRC for financial support (studentship to R.B.O.) and the SOCRATES European student exchange program (P.T.). We also thank Prof. Viresh Rawal (University of Chicago) for useful suggestions.

Supporting Information Available: General experimental procedures and representative procedures for 4 + 3 cycloaddition reactions/Favorskii rearrangements. Copies of ^1H and ^{13}C NMR spectra for all compounds used in this study. X-ray data for compound **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Selective 1,5-Alkylidenecarbene Insertion Reactions on [3.2.1] Oxabicyclic Ethers: A New Approach toward the AB Ring System of Ingenol

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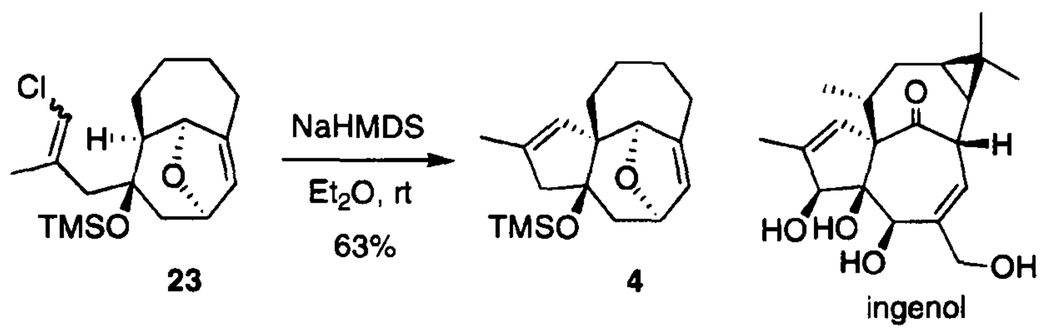
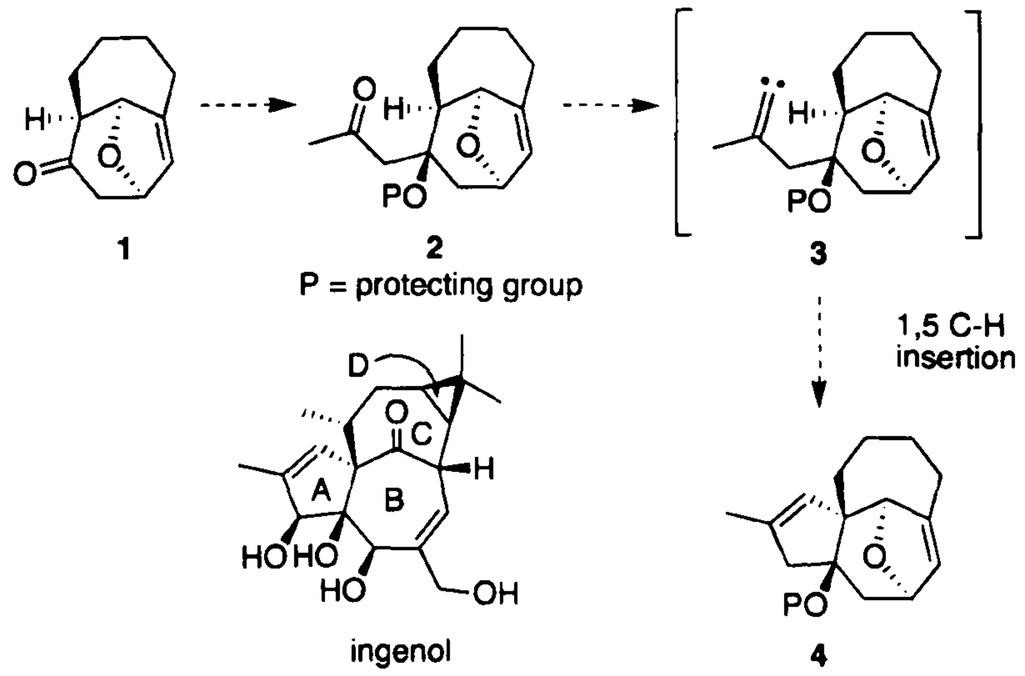
ABSTRACT



Two methods to achieve the formal aldol reaction between acetone and two oxabicyclic [3.2.1] ketones are reported. The trimethylsilyl-protected β-hydroxy ketones are converted by a Wittig reaction into vinyl chlorides as synthetic precursors to alkylidenecarbenes. Selective 1,5 C–H over 1,5 O–Si insertion has been applied to the synthesis of a model for the ABC ring system of ingenol.

Alkylidenecarbenes, or alkenylidenes, are versatile intermediates for organic synthesis.[1] We are interested in the selective 1,5 C−H insertion of alkylidenecarbenes as a means to construct the A-ring of ingenol (Scheme 1).[2,3] Two particular features of the 1,5 C−H insertion reaction appear to be particularly attractive in this context. First, alkylidenecarbenes are known to selectively insert into tertiary over secondary C−H bonds.[4] Second, the reaction has been shown to proceed with retention of configuration at the C−H bond at a stereocenter.[5] This we deem particularly important in terms of the trans BC ring junction of ingenol, which has been shown to be both thermodynamically less favorable than the cis configuration and also critical for the biological

Scheme 1. Alkylidenecarbene Insertion Strategy



(1) For a review of early work, see: Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.

(2) For recent representative examples of 1,5 C−H insertion reactions of alkylidenecarbenes, see: (a) Ohira, S.; Fujiwara, H.; Maeda, K.; Habara, M.; Sakaedani, N.; Akiyama, M.; Kuboki, A. *Tetrahedron Lett.* **2004**, *45*, 1639. (b) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768. (c) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096. (d) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609. (e) Wardrop, D. J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (f) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613. (g) Walker, L. F.; Bourghida, A.; Connolly, S.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 965. (h) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011. (i) Ohira, S.; Kuboki, A.; Hasegawa, T.; Kikuchi, T.; Kutsukake, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 4641. (j) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. For other methods for C−H bond activation, see: (k) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900 and references therein.

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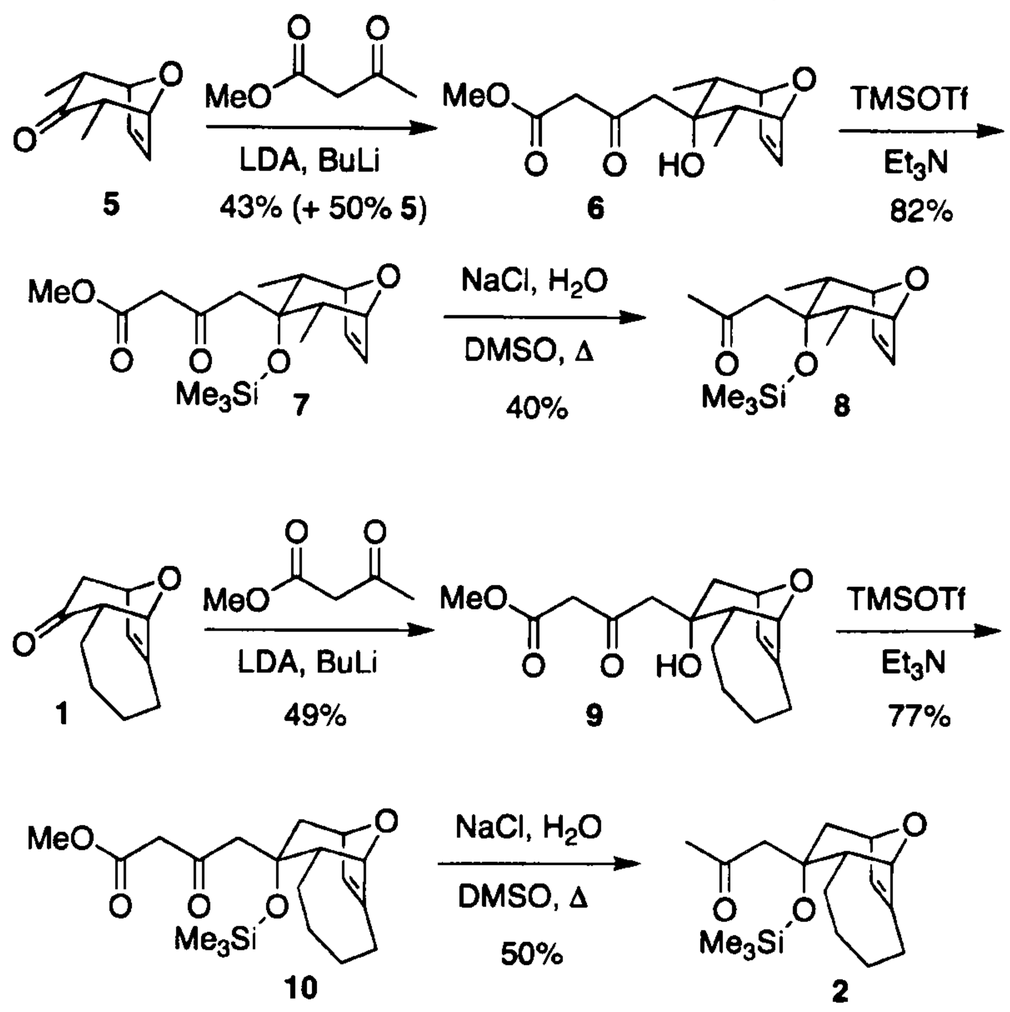
activity of the natural product.[6] Any strategy therefore that establishes this stereochemical feature must also be coupled with a compatible method for installing the A-ring. Herein we report the first examples of alkylidenecarbene 1,5 C−H insertion chemistry on the [3.2.1] oxabicyclic skeleton as models for the AB ring system of ingenol, an approach that also overrides the "usual" preference for alkylidenecarbenes to undergo 1,5 O−Si insertion over 1,5 C−H insertion.[7]

We have recently reported the synthesis of oxatricyclic ketone **1** as a model for the BC ring system of ingenol, where it is anticipated that stereoselective reduction of the alkene offers a potential route to the *trans*-ring junction (Scheme 1).[3k] Installation of the A-ring onto this system can in principle be achieved by a selective 1,5 C−H insertion reaction of an alkylidenecarbene **3** into the tertiary axial C−H bond over the axial or equatorial secondary C−H bonds. Alkylidenecarbene **3** could be generated from ketone **2**, the product of a face-selective aldol reaction between ketone **1** and the enolate of acetone, followed by protection of the alcohol. However, while such an approach can deliver the requisite bridgehead oxygen at the AB ring juncture, it also opens up the possibility of an alternative undesired reaction pathway, formal insertion of the alkylidenecarbene into the O−P bond leading to dihydrofuran formation. Although such a reaction pathway is generally favored over the 1,5 C−H insertion pathway,[7] we felt that structural features present in **3** might disfavor this pathway sufficiently to warrant further investigation (vide infra).

Addition of nucleophiles to [3.2.1] oxabicyclic ketones has been extensively investigated. In general, preferential addition syn to the oxygen bridge is observed.[8] We are not aware, however, of any examples of direct enolate addition to such ketones. Taking the readily prepared **5** as a representative oxabicyclic ketone,[9] a number of attempts were made to add the enolate of acetone[10] under various conditions, without success. A more reactive enolate in the form of the dianion of methyl acetoacetate could be added, although the yields were only moderate (Scheme 2).[11] β-Keto ester **6** could be protected and decarboxylated to provide ketone **8**.[12]

Scheme 2. Addition of Dienolates to Oxabicyclic Ketones



An identical sequence of reactions on oxatricyclic ketone **1** gave the protected β-hydroxy ketone **2**, albeit again in only moderate yield.

The low yield for the enolate addition step in the above reaction made us consider alternative strategies based on addition of a suitable organometallic reagent that could subsequently be converted into an alkylidenecarbene precursor such as a vinyl halide. Taber has reported a bromination−dehydrobromination strategy for the conversion of terminal alkenes to vinylbromides.[13]

Toward this end, we added 2-methylallyl Grignard to ketones **5** and **1** at −78 °C to give the axial alcohols **11** and **13**, respectively (Scheme 3). However, selective bromination of the terminal alkene (Br_2, Et_2O, −78 °C) was thwarted by the higher reactivity of the internal alkene. Although ultimately not suitable for our purpose, this reactivity could be exploited for high-yielding syntheses of the unusual bromoethers **12** and **14**, which also pointed to the close

(3) Total syntheses of ingenol: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. For a review of approaches to the synthesis of ingenol, see: (c) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. For more recent work, see: (d) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032. (e) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265. (f) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296. (g) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927. (h) Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563. (i) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799. (j) Mislin, G. L.; Miesch M. *J. Org. Chem.* **2003**, *68*, 433. (k) Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. *J. Org. Chem.* **2003**, *68*, 7899.

(4) Relative rates of insertion methine > methylene > methyl can be influenced by the presence of adjacent heteroatoms and by the method used to generate the alkylidenecarbene. See, for example: Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927.

(5) (a) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251. (b) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.

(6) A highly functionalised cis-fused analogue of ingenol has been shown to be devoid of biological activity: Paquette, L. A.; Ross, R.; Springer, J. *J. Am. Chem. Soc.* **1988**, *110*, 6192.

(7) (a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 461. (b) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1995**, *36*, 4845. (c) Feldman, K. S.; Wrobleski, M. L. *J. Org. Chem.* **2000**, *65*, 8659. (d) Hobley, G. H.; Stuttle, K.; Wills, M. *Tetrahedron* **2003**, *59*, 4739. (e) Gais, H.-J.; Reddy, L. R.; Babu, G. S.; Raabe, G. *J. Am. Chem. Soc.* **2004**, *126*, 4859. See also ref 2c.

(8) (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Chiu, P.; Lautens, M. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer-Verlag: New York, 1997; Vol. 190, pp 1−85. (c) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934.

(9) Lautens, M.; Bouchain, G. *Org. Synth.* **2002**, *79*, 251.

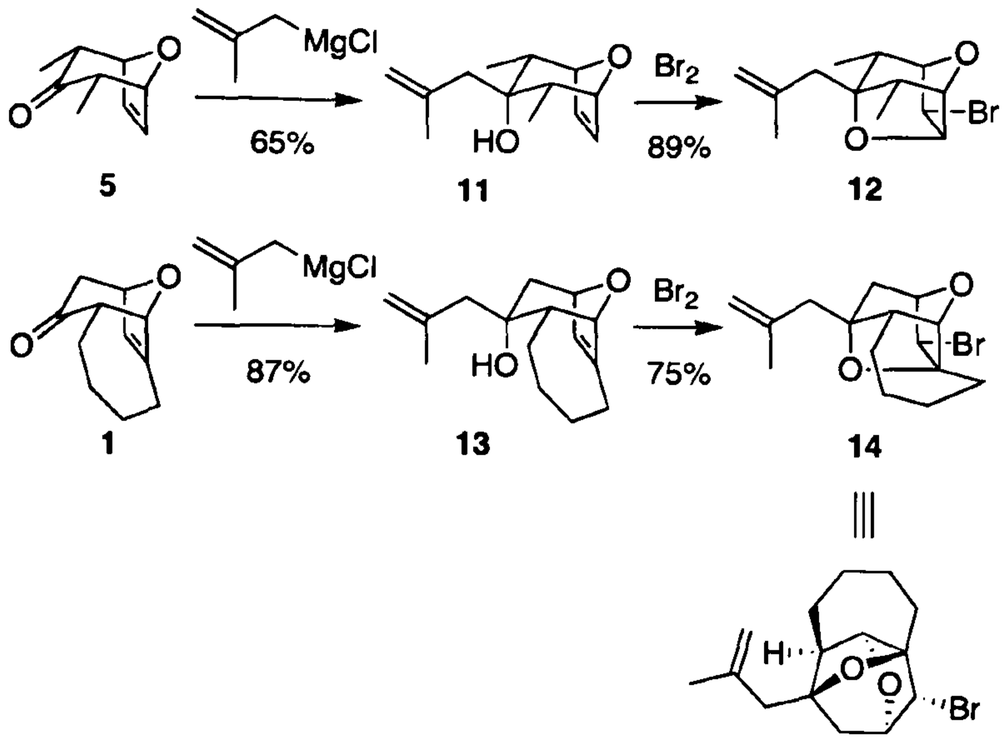
(10) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Basbas, C. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 7283.

(11) While this manuscript was being prepared, Chiu reported the high-yielding addition of the dianion of ethylacetoacetate to oxabicyclic ketone **5**: Chiu, P.; Zhang, X.; Ko, R. Y. Y. *Tetrahedron Lett.* **2004**, *45*, 1531.

(12) Attempted decarboxylation prior to protection results in reformation of ketone **5**.

(13) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673.

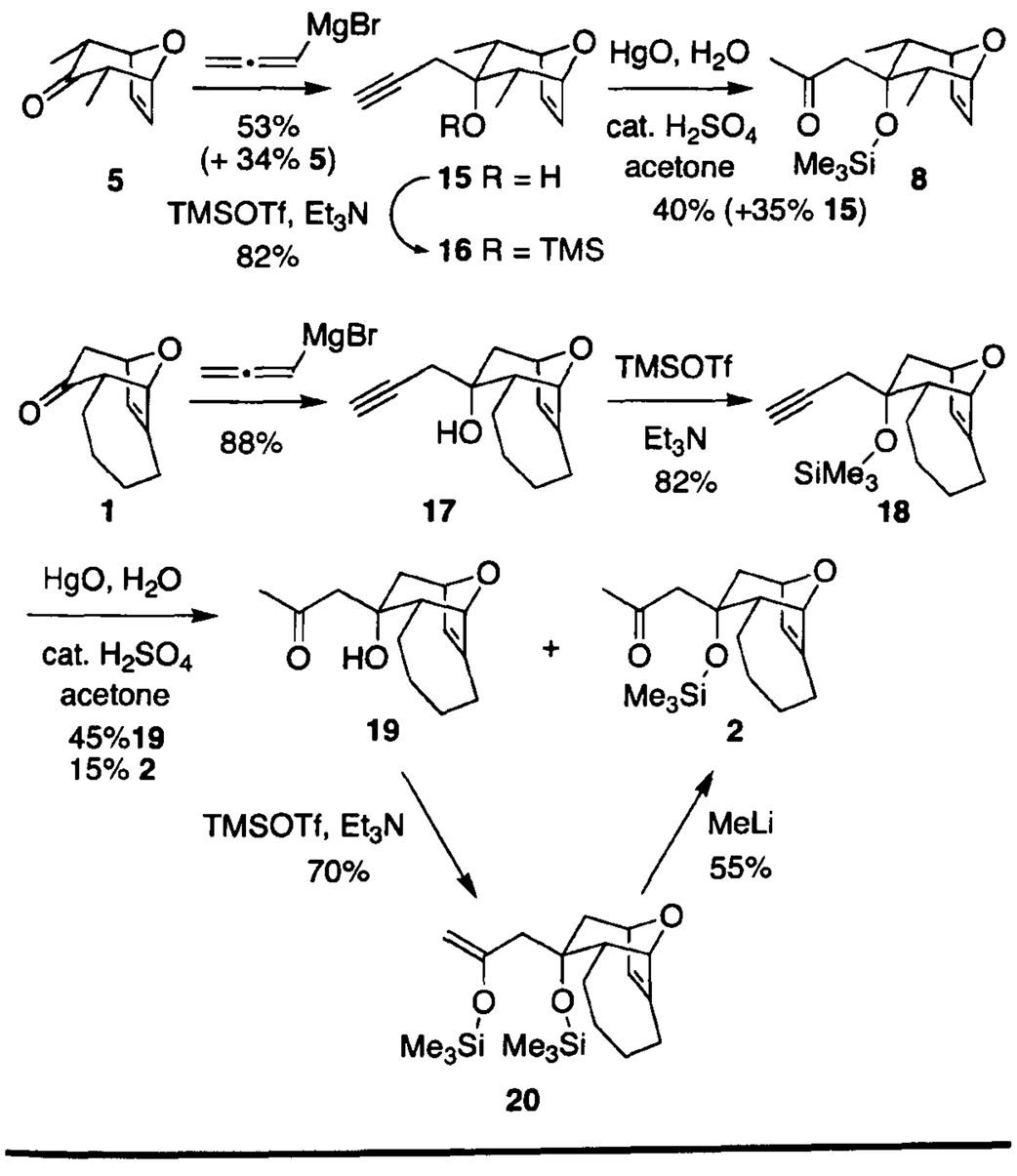
Scheme 3. Intramolecular Haloetherification



proximity of the axial-orientated alcohol to the internal double bond.[14] Interestingly, compound **14** contains a trans arrangement in the [4.4.1] carbocyclic system.

Addition of allenyl Grignard[15] was also successful (Scheme 4). After protection of the alcohol as a trimethylsilyl ether,

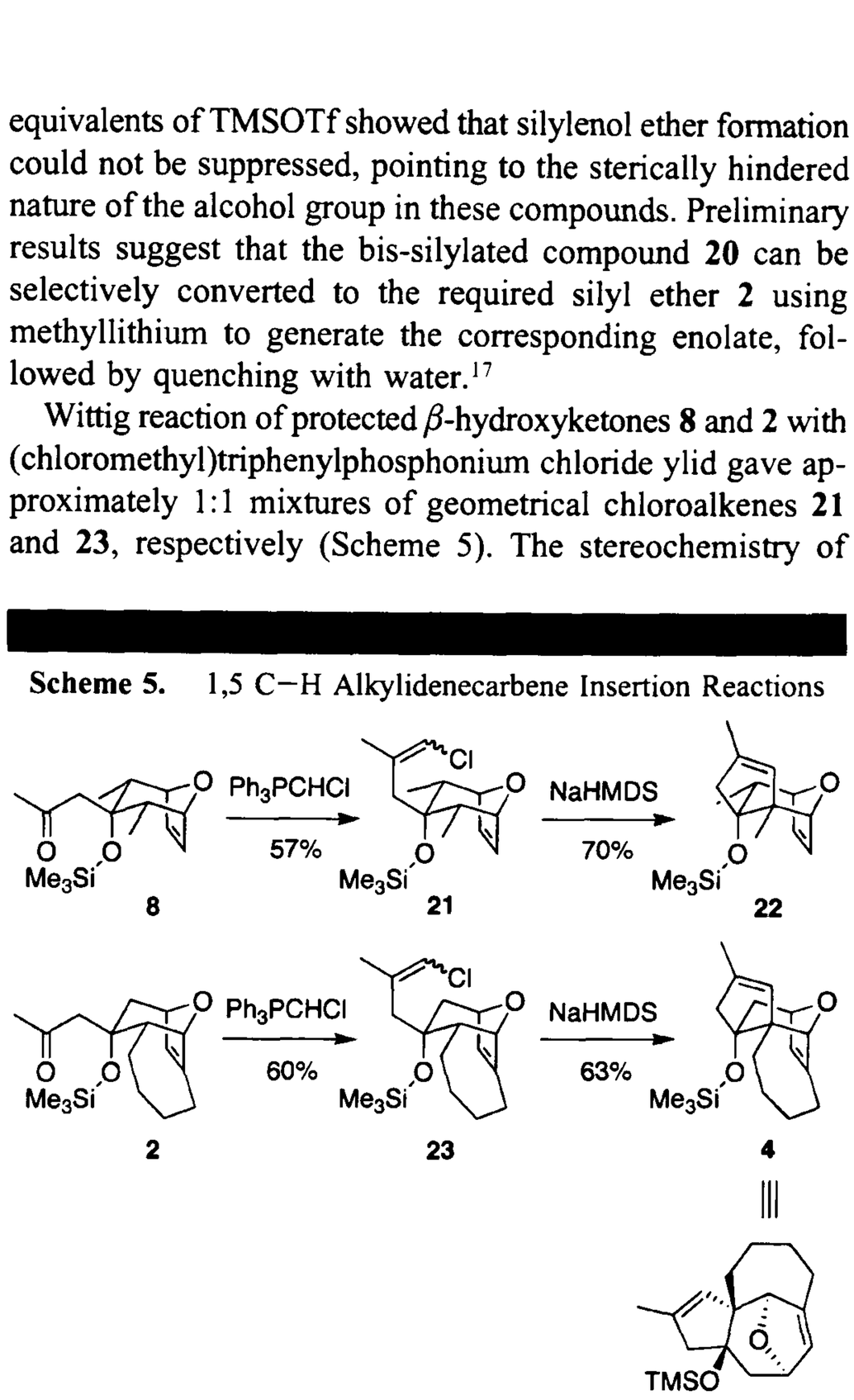
Scheme 4. Formation of β-Silyloxyketones via Alkyne Hydrolysis



selective hydrolysis of the terminal alkyne could be achieved,[16] although this reaction was accompanied by significant amounts of silyl deprotection in the case of the tricyclic system **18**. Reprotection of the β-hydroxyketone **19** under standard conditions gave the doubly silylated product **20**. Attempts to limit the formation of **20** by reducing the equivalents of TMSOTf showed that silylenol ether formation could not be suppressed, pointing to the sterically hindered nature of the alcohol group in these compounds. Preliminary results suggest that the bis-silylated compound **20** can be selectively converted to the required silyl ether **2** using methyllithium to generate the corresponding enolate, followed by quenching with water.[17]

Wittig reaction of protected β-hydroxyketones **8** and **2** with (chloromethyl)triphenylphosphonium chloride ylid gave approximately 1:1 mixtures of geometrical chloroalkenes **21** and **23**, respectively (Scheme 5). The stereochemistry of

Scheme 5. 1,5 C−H Alkylidenecarbene Insertion Reactions



these chloroalkenes proved to be irrelevent: both isomers gave rise to the same product of 1,5 C−H alkylidenecarbene insertion (cyclopentenes **22** and **4**, respectively) upon exposure to sodium bis(trimethylsilyl)amide at room temperature in diethyl ether.[18] In the case of chloroalkene **23**, complete selectivity for insertion into a tertiary axial C−H bond over a secondary axial or equatorial C−H bond is observed.

Alkylidenecarbenes are known to undergo intramolecular 1,5 O−Si insertion reactions to yield 2,3-dihydrofuran derivatives, and this pathway has been shown to proceed more rapidly than 1,5 C−H insertion.[7,19] Notably in the case of both **21** and **23**, we have not observed any products arising from this potentially competing reaction. The mechanism of such reactions can proceed via two possible pathways,

(14) Stereochemistry of **12** and **14** are assigned on the basis of attack of Br_2 on the less hindered *exo*-face of the internal alkene, followed by intramolecular capture of the bromonium ion intermediate by the axial alcohol.

(15) Hopf, H.; Böhm, I.; Kleinschroth, J. *Org. Synth.* **1981**, *60*, 41−48.

(16) Jacobi, P. A.; Herradura, P. *Tetrahedron Lett.* **1997**, *38*, 6621.

(17) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.

(18) Geometrical chloroalkenes are separable in the case of **21**. We have observed that (*E*)-**21** cyclizes faster than (*Z*)-**21** under identical reaction conditions.

(19) An exception is seen in the work of Wills, whereby 1,5 C−H insertion into the activated methylene of a benzylic ether is preferred over 1,5 O-TBS insertion. However, a MOM methylene CH is less likely to undergo insertion than an O-TBS. See ref 7d.

concerted O−Si insertion or, more likely, an initial interaction of the vacant orbital on the carbene with an oxygen lone pair to produce a transient oxonium ylide,[20] which undergoes a subsequent 1,2 silyl migration. Should the latter indeed be the case, then the absence of products derived from 1,5 O−Si insertion can be ascribed to the need to adopt an unfavorable conformation **I** or **III** in order to achieve orbital overlap (Figure 1, illustrated for the case of **21**). In particular, the

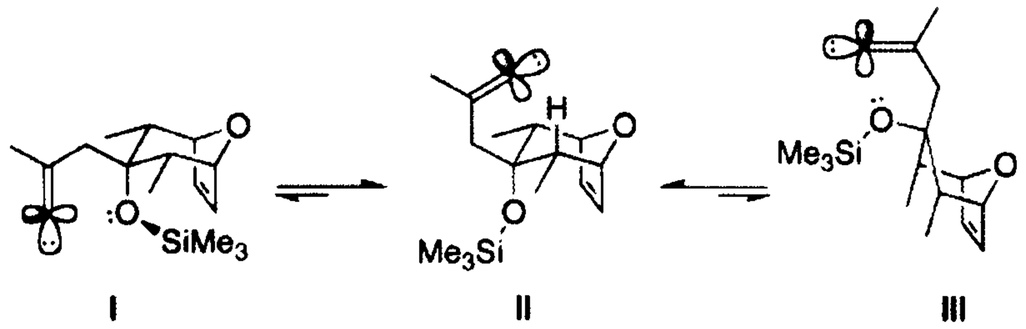


Figure 1. Conformational control of 1,5 alkylidenecarbene insertion.

bulky trimethylsilyl group is expected to be orientated *exo* to the oxabicyclic ring system in the lowest energy conformation **II**, placing the lone pairs on oxygen in an *endo* orientation where they are unable to interact with the alkylidenecarbene and hence allowing the 1,5 C−H insertion pathway to dominate.[21]

In conclusion, two methods for the preparation of alkylidenecarbene precursors based on nucleophilic attack on [3.2.1] oxabicyclic ketones have been developed. Selective insertion into a bridgehead tertiary C−H bond has been used to generate a model for the ABC ring system of ingenol and more generally for the preparation of cis-fused perhydrozulenes. Further studies on incorporating this chemistry in a synthesis of a trans intrabridgehead ring system related to ingenol are ongoing.

Acknowledgment. We thank EPSRC and King's College London for funding this work and AstraZeneca and Pfizer for additional financial support.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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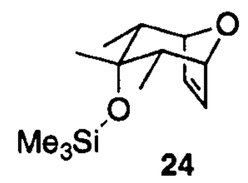
(20) Sueda T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.

(21) We have carried out molecular mechanics calculations on the simplified model compound **24** using the Sybyl force field in Spartan IBM Version 5.1.3 X11 (Wavefunction, Inc). Geometry optimization for both chair and boat conformations show the lowest energy boat conformation to be 7.9 kcal/mol higher in energy than the chair. In both cases, the trimethylsilyl group is orientated gauche to the methyl group around the carbon−oxygen bond (CH_3−C−O−Si dihedral angle 51.1° for chair and 52.2° for boat). Rotation about this carbon−oxygen bond in the chair form shows a conformation where the lone pair and methyl group are synperiplanar to be 6.1−6.5 kcal/mol higher in energy than the lowest energy gauche conformation. Similarly, in the boat form, the synperiplanar orientation of methyl and the oxygen lone pair is 5.5 kcal/mol higher in energy than the gauche conformation.



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